REMARKS

Claims 1-25 are pending in the subject application. Applicant has added new claims 26 and 27. Accordingly, upon entry of this amendment, claims 1-27 will be pending.

Support for new claim 26 may be found, *inter alia*, in the specification at page 21, line 7 and lines 10-12.

Support for new claim 27 may be found, *inter alia*, in the specification at page 15, lines 16 to 17; and page 17, line 31.

Support for new claim 28 may be found, *inter alia*, in the specification at page 15, lines 16 to 17; and page 18, lines 5-6.

Support for new claim 29 may be found, *inter alia*, in the specification at page 15, lines 16 to 17.

Claim Rejections - 35 USC § 103(a)

In the April 9, 2009 Office Action, the Examiner rejected claims 1-25 under 35 U.S.C. § 103(a) as allegedly unpatentable over Szabo et al. (U.S. Patent No. 6,531,464) in view of Arnon et al. (U.S. Patent No. 6,214,791) and Kerwar et al. (U.S. Patent No. 4,617,319).

Specifically, the Examiner alleged that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use a combination composition comprising the active agents glatiramer acetate and mitoxantrone for the treatment of a subject afflicted with multiple sclerosis in Szabo et al. because:

- Szabo et al. disclose administration of the combination of glatiramer acetate and mitoxantrone (claim 10, i.e.

"administering one or more additional agents for treating symptoms associated with multiple sclerosis"; and claim 11, as two of only five specifically contemplated "additional agents" also capable of treating multiple sclerosis) (The Examiner cited the entire document, especially claims 10-11);

- Arnon et al. disclose the use of glatiramer acetate as the primary agent for the treatment of multiple sclerosis, in a therapeutically effective amount through any means of administration (The Examiner cited the entire document, especially claims 1 and 8; col. 1, lines 35-41; and Fig. 8); and

- Kerwar et al. disclose the use of mitoxantrone (TradeName NOVANTRONE) as the primary agent for the treatment of multiple sclerosis, in a therapeutically effective amount through any means of administration (The Examiner cited the entire document especially claim; col. 1; lines 5-9).

Based on the combination of references, the Examiner alleged that,

> "It would have been predictable to one of ordinary skill in the art, at the time of the invention, to effectively administer the **exclusive** combination of glatiramer acetate and mitoxantrone, as primary agents (rather than only additional/secondary agents) for the treatment of multiple sclerosis in SZABO et al., because ARNON et al. teach the advantageous use of glatiramer acetate as the primary agent for the treatment of multiple sclerosis and KERWAR et al. teach the advantageous use of mitoxantrone (TradeName NOVANTRONE) as the primary agent for the treatment of multiple sclerosis..." (emphasis added, see bottom of page 3 to top of page 4 of the April 3, 2009 Office Action).

The Examiner asserted that it is apparent from the references above that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. The

Examiner alleged that the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's Response

In response, applicant respectfully traverses the obviousness rejection for each of the following reasons independently.

Initially, the Examiner has misinterpreted claims 10 and 11 of Szabo et al. Specifically, these claims cannot be interpreted to disclose a combination treatment of glatiramer acetate and mitoxantrone. A proper construction of claim 11 indicates a disclosure of only one member of the group. This is well settled patent law. See, e.g. Abbott Laboratories v. Baxter Pharmaceutical Products, Inc., 334 F.3d 1274, 1281, 67 USPQ2d 1191, 1196 (Fed.Cir.2003), attached hereto as **Exhibit 1**, holding that "'a' with 'consisting of' in this case indicates only one member of a Markush group. *See KJC Corp.*, 223 F.3d at 1356. If a patentee desires mixtures or combinations of the members of the Markush group, the patentee would need to add qualifying language while drafting the claim…". Claim 11 of Szabo et al. clearly fails to recite any qualifying language and, thus, clearly fails to support the Examiner's erroneous construction. In fact, claim 11 of Szabo et al. requires that no more than one member from the group is to be selected for administration. Accordingly, the prior art fails to teach or suggest combining mitoxantrone and glatiramer acetate for treatment of multiple sclerosis.

Furthermore, the administration of two different drugs to treat a given condition, such as a form of multiple sclerosis, raises a number of potential problems (see pages 4, line 26 to page 5, line 29 of the subject application). Specifically, it is well accepted

that "when two drugs are administered to treat the same condition, it is unpredictable whether each will complement, have no effect on, or interfere with the therapeutic activity of the other in a human subject." (see page 5, lines 3-7 of the subject application; Guidance for Industry. *In vivo* drug metabolism/drug interaction studies study design, data analysis and recommendations for dosing and labeling); "upon administration of two drugs to treat a disease, it is unpredictable what change will occur in the negative sideprofile of each drug." (see page 5 lines 15-16 of the subject application; Guidance for Industry. *In vivo* drug metabolism/drug interaction studies study design, data analysis and recommendations for dosing and labeling); and "it is accurately difficult to predict when the effects of interaction between the two drugs will become manifest." (see page 5, lines 18-20 of the subject application; Guidance for Industry. *In vivo* drug metabolism/drug interaction studies study design, data analysis and recommendations for dosing and labeling). Accordingly, the prior art does not predict success when administering two drugs for a given disease.

In fact, the prior art shows that unanticipated side effects can occurs when two drugs are combined. For example, in the case of natalizumab and interferon β-1a, the combination was abserved to increase the risk of unanticipated side effects (see Vollmer et al., page 1, bottom of 2nd column to page 2, top of first column; attached hereto as **Exhibit 2**).

Yet furthermore, applicant has made the unexpected observation that immunosuppression with mitoxantrone accelerates and enhances the efficacy of glatiramer acetate administered to the patient (see instant claim 29; page 15, lines 15-18 of the subject application; and page 2, 2nd column, last full paragraph and page 7, 2nd column, last paragraph ending on page 8 of Vollmer et al.).

In addition, the enhancement of glatiramer acetate treatment is

demonstrated by a significant reduction in both the accumulation of Gd-enhancing lesions and in the mean relapse rate (see instant claims 26-28 and Vollmer et al., page 5, bottom of 2nd column to page 6, 2nd column, first full paragraph).

The prior art provides no evidence or even suggestion that treatment with mitoxantrone would enhance the efficacy of glatiramer acetate in general or by reducing the accumulation of Gd-enhancing lesions or mean relapse rate.

Applicant also notes that predictability must be analyzed taking into account views of those skilled in the art at the time the invention was made. As discussed above, the FDA clearly outlined the known obstacles to predicting the effects of administration of a combination of two drugs to treat a given condition (see Guidance for Industry. *In vivo* drug metabolism/drug interaction studies study design, data analysis and recommendations for dosing and labeling). In addition, the instant invention is based on clinical trials conducted in human subjects as performed by Dr. Vollmer and co-authors verifying the claimed combination is not subject to unexpected side effects, such as e.g. natalizumab and interferon β-1a, as discussed in the paragraph bridging page 7 and 8 of Vollmer et al. Of note is that the results and skepticism of Vollmer et al. have been published in a peer-reviewed international journal i.e., *Multiple Sclerosis*. Accordingly, contrary to the Examiner's assertion, the state of the art and the opinion of skilled artisans show that applicants' claimed invention is not predictable.

The Supreme Court of the United States most recently reaffirmed that the obviousness inquiry must be based on knowledge at the relevant time and continually cautioned against slipping into hindsight reconstruction. See, *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385, 1391 (2007), attached hereto as **Exhibit 3**. The *KSR* Court reiterated the need for a fact

finder to be aware "of the distortion caused by hindsight bias" and to "be cautious of arguments reliant upon ex post reasoning." *KSR*, 82 U.S.P.Q.2d at 1397.

Factors such as uncertainty and lack of predictability in the field at the time of the invention must be considered. *See, e.g. KSR*, 82 U.S.P.Q.2d at 1396. At least some degree of predictability is required in the prior art to render an invention obvious. *See, also, In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988), attached hereto as **Exhibit 4**. Even if there was a general suggestion or motivation to attempt to produce the invention, uncertainty and lack of predictability in the field will render the invention patentable and not obvious. *See*, M.P.E.P. § 2143.02; *In re Vaeck*, 947 F.2d 488, 495, 20 U.S.P.Q.2d 1438, 1444 (Fed. Cir. 1991); *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1207-08, 18 U.S.P.Q2d 1016, 1022-23, (Fed. Cir. 1991), attached hereto as **Exhibits 5, 6 and 7**. (Holding invention non-obvious even though it was "obvious to try" because lack of predictability in the biotechnology field eliminated reasonable expectation of success). The Federal Circuit recently instructively explained in *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 533 F.3d 1353, at 1359 (Fed. Cir. 2008), attached hereto as **Exhibit 8** that, "[t]o the extent an art is unpredictable, as the chemical arts often are, *KSR's* focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." (Emphasis added)

In conclusion, applicant submits that Szabo et al. do not disclose the co-administration of mitoxantrone and glatiramer acetate for the treatment of multiple sclerosis as recited in the pending claims. Moreover, neither Arnon et al. nor Kerwar et al. provide any motivation or guidance to predictably overcome the known obstacles to predicting the effects of a combination of two drugs to treat a given condition. Thus, none of the Examiner's cited

references, alone or in combination, support the obviousness rejection.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than $130.00 fee for a one-month extension of time and $208.00 for 4 new claims is deemed necessary in connection with the filing of this response. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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Gary J. Gershik 8/3/09
Gary J. Gershik Date
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Exhibit 1

ies, and affiliated companies, the successors and assigns of said companies and individuals, and the officers, directors, agents, partners, servants, employees, and attorneys of all of them and all others in active concert or participation with them, are permanently enjoined and restrained from: (a) using the ADVANTAGE mark. any mark similar thereto, or any other mark owned by Bayer Corporation, in connection with the importation, sale, distribution, advertising or promotion of any products or services; (b) selling ADVANTAGE products through any and all channels of trade including but not limited to the Internet; (c) using the ADVANTAGE mark, any mark similar thereto, or any other mark owned by Bayer Corporation, on or in connection with or as part of any web site, metatags or other computer code or otherwise in connection with the retrieval of data or information (including without limitation the use of such terms as keyword or keywords in pay-for-placement or pay-for-rank search engines) or in connection with the advertising or promotion of any goods, services or web sites; (d) reproducing or otherwise using any graphics, images or other copyrightable material owned by Bayer Corporation; (e) registering or using any domain names similar to the *nofleas.com* domain name, the ADVANTAGE mark, or any other mark or domain name owned by Bayer Corporation; and (f) committing any act that dilutes or tarnishes Bayer Corporation's ADVANTAGE mark or tarnishes or injures Bayer Corporation's business reputation;

3. Defendants shall transfer ownership and possession of the *no-fleas.com* domain name to Bayer Corporation within ten (10) days of the entry of this order by ensuring that all maintenance fees are paid through the date of such transfer to Bayer Corporation, completing all forms necessary to achieve this transfer, and working with Bayer Corporation until this transfer is complete; and,

4. Within thirty (30) days of this order, Defendants shall request the removal of any and all entries, records and registrations of the *www.no-fleas.com* web site, the ADVANTAGE mark and any search terms and keywords associated therewith, with all Internet search engines previously identified and agreed upon in writing by the parties.

SO ORDERED AND ADJUDGED:

Abbott Laboratories v. Baxter Pharmaceutical Products Inc.

U.S. Court of Appeals
Federal Circuit

No. 02-1400

Decided July 3, 2003

PATENTS

[1] Patentability/Validity — Anticipation — Prior art (§ 115.0703)

Patent construction — Patent office proceedings (§ 125.05)

Patent construction — Claims — Broad or narrow (§ 125.1303)

Patentee, in disclosing to U.S. Patent and Trademark Office its prior sale of sevoflurane anesthetic in specific glass container with water content up to 131 parts per million, did not disavow or relinquish all water concentrations below 131 ppm for method claim directed to sevoflurane containing water in "amount sufficient" to prevent degradation by Lewis acids, since specification teaches that effective amount of Lewis acid inhibitor will vary depending upon conditions to which sevoflurane is subjected, including temperature and type of container in which it is stored, since mere submission of invention disclosure statement to PTO does not constitute admission that anything in IDS is material prior art, and since examiner did not consider prior sale relevant, and patentee did not distinguish claims over disclosed sale.

[2] Patent construction — Specification and drawings — Defining terms (§ 125.1103)

Patent construction — Claims — Broad or narrow (§ 125.1303)

Statements in specification that "effective amount" of water ranges from about 150 parts per million to saturation level do not limit scope of method claim directed to sevoflurane anesthetic containing water in "amount sufficient" to prevent degradation by Lewis acids, since statements refer only to narrow preferred embodiments of invention, not to invention as whole, since specification does not indicate that applicant restricted claims to preferred embodiments, and these descriptions do

not amount to express disavowal of other effective amounts, and since applicant, in overcoming prior art rejection during prosecution, did not cite examples in its specification as only specified water amounts that are "effective" to inhibit Lewis acids.

[3] Patent construction — Prosecution history estoppel (§ 125.09)

Patent construction — Claims — Broad or narrow (§ 125.1303)

Plain meaning of asserted claims directed to sevoflurane anesthetic containing "a Lewis acid inhibitor" limits claims to single Lewis acid inhibitor selected from Markush group recited in claims, since patentee, without expressly indicating selection of multiple members of Markush grouping, does not claim anything other than plain reading of closed claim language, and since claims at issue do not contain such express indication; prosecution history supports this construction, since applicant added Markush group reciting certain Lewis acid inhibitors in order to comply with requirements of 35 U.S.C. § 112 and gain allowance, and in doing so, applicant disclaimed any coverage for inhibitors other than listed members of Markush groups in issued claims.

[4] Patentability/Validity — Anticipation — Prior sale — In general (§ 115.0707.01)

Patent construction — Claims — Broad or narrow (§ 125.1303)

Federal district court erred by narrowly construing method claims directed to sevoflurane anesthetic containing water in "amount sufficient" to prevent degradation by Lewis acids in order to preserve their validity in view of plaintiff's prior art sale of sevoflurane, since court expressly declined to determine validity of claims, and parties did not raise issue of validity, and since court did not have evidence that plaintiff's sale of sevoflurane constituted prior art to claimed invention; plaintiff's mere disclosure of sale to U.S. Patent and Trademark Office during prosecution did not constitute admission that sale was material prior art.

Particular patents — Chemical — Sevoflurane anesthetic

5,990,176, Bieniarz, Chang, Cromack, Huang, Kawai, Kobayashi, Loffredo, Raghavan, Speicher, and Stelmach, fluoroether compositions and methods for inhibiting their degradation in the presence of a Lewis acid, summary judgment of noninfringement vacated.

Appeal from the U.S. District Court for the Northern District of Illinois, Guzman, J.

Action by Abbott Laboratories and Central Glass Co. Ltd. against Baxter Pharmaceutical Products Inc. and Baxter Health Care Corp. for patent infringement. Plaintiff appeals from summary judgment of noninfringement. Vacated and remanded.

R. Mark McCareins, Edward L. Foote, Raymond C. Perkins, Peggy Balesteri, Blake T. Hannafan, and James F. Herbison, of Winston & Strawn, Chicago, Ill., for plaintiffs-appellants.

Constantine L. Trela Jr., David T. Pritikin, William H. Baumgartner Jr., Hugh A. Abrams, and Russell E. Cass, of Sidley Austin Brown & Wood, Chicago; Thomas S. Borecki, of Baxter Healthcare Corp., Deerfield, Ill., for defendants-appellees.

Before Rader, Gajarsa, and Dyk, circuit judges.

Rader, J.

Plaintiffs-Appellants, Abbott Laboratories and Central Glass Company, Ltd. (collectively, Abbott), appeal the district court's grant of Defendants-Appellees Baxter Pharmaceutical Products, Inc. and Baxter Health Care Corp.'s (Baxter) motion for summary judgment of noninfringement. *Abbott Labs v. Baxter Pharm. Prods.*, No. 01-CV-1867, 2002 WL 449007 (N.D. Ill. Mar. 22, 2002). Because the district court erred in construing the asserted claims, this court vacates the district court's decision and remands for further adjudication.

I.

Abbott owns U.S. Patent No. 5,990,176 (the '176 patent), filed January 27, 1997, and issued November 23, 1999. The '176 patent claims compositions and methods of preventing the degradation of sevoflurane anesthetic by adding an effective amount of certain specific Lewis acid inhibitors. Abbott filed the '176 patent application after discovering that these Lewis acid inhibitors protected the shelf

life of sevoflurane. Lewis acids attack sevoflurane at its ether and halogen linkages, thereby releasing hydrofluoric acid (HF) into the anesthetic. Because HF corrodes skin and mucous membranes, its presence in an anesthetic is harmful. HF also etches glass, and thus, exposes sevoflurane in glass vessels to additional Lewis acids and glass particles. Therefore, the '176 patent improved the storage and use of sevoflurane.

Baxter filed an Abbreviated New Drug Application (ANDA) with the Food and Drug Administration (FDA) proposing to market generic sevoflurane. Baxter's proposed product is a composition containing sevoflurane anesthetic with not more than 130 ppm water. Baxter also proposes to contain the composition in an aluminum vessel coated with an epoxyphenolic resin liner. In its application to the FDA, Baxter made a paragraph IV certification that its proposed generic sevoflurane product does not infringe the '176 patent. Thereafter, Abbott filed this suit alleging infringement of the '176 patent. At issue are independent claims 1, 6, and 10 of the '176 patent (emphases added):

Claim 1.

An anesthetic composition comprising: a quantity of sevoflurane; and

> *a Lewis acid inhibitor* in an *amount effective* to prevent degradation by a Lewis acid of said quantity of sevoflurane, said Lewis acid inhibitor *selected from the group consisting of* water, butylated hydroxytoluene, methylparaben, propylparaben, propofol, and thymol.

Claim 6.

A method of preventing degradation by a Lewis acid of a quantity of sevoflurane, the method comprising the steps of:

> providing a quantity of sevoflurane;
>
> providing *a Lewis acid inhibitor* in an *amount sufficient* to prevent degradation by a Lewis acid of said quantity of sevoflurane, said Lewis acid inhibitor *selected from the group consisting of* water, butylated hydroxytoluene, methylparaben, propylparaben, propofol, and thymol; combining said quantity of sevoflurane and the Lewis acid inhibitor in an amount sufficient to prevent the degradation by a Lewis acid of said quantity of sevoflurane.

Claim 10.

A method of preventing degradation by a Lewis acid of a quantity of sevoflurane, the method comprising the steps of:

> providing a quantity of sevoflurane;
> providing water in an *amount sufficient* to prevent degradation by a Lewis acid of said quantity of sevoflurane;
> combining said quantity of sevoflurane and said water in an *amount sufficient* to prevent the degradation by a Lewis acid of said quantity of sevoflurane.

During prosecution of the '176 patent application, Abbott filed an Information Disclosure Statement (IDS) with the United States Patent and Trademark Office (USPTO). The IDS listed a reference indicating that at least one year before the filing date of the '176 patent, Abbott sold sevoflurane in glass bottles with a water content up to 131 ppm. Baxter seized upon this disclosure as a limit on the scope of the claims. Therefore, Baxter asserted that its generic sevoflurane with a water content of no more than 130 ppm falls within the prior art and does not infringe the '176 patent.

The district court agreed. Specifically, the district court construed the claim terms "amount effective" and "amount sufficient" of independent claims 1 and 6 to mean amounts above 131 ppm of water. Citing the '176 patent at column 4, lines 31-34, 45-47, and 56-58, the district court noted that the specification teaches that an effective stabilizing amount of Lewis acid inhibitor that " 'can be used' or 'is believed to be' 'about 0.150%w/w' (150ppm)." The district court acknowledged: "[N]othing in the specifications [sic] inherently requires the amount of water to be 150 ppm or more." The district court said it was "prepared to decline to limit its interpretation of the terms 'effective' or 'sufficient' amount to 150 ppm or greater but for Baxter's argument that the prosecution history of the '176 patent shows a prior sale which must limit the claims of the patent, lest it be invalid under 35 U.S.C. § 102(b)." *Abbott*, 2002 WL 449007, at *4. Accordingly, the district court limited the claim terms "effective amount" and "amount sufficient" to water content above 131 ppm.

Based on this construction, the district court granted summary judgment of noninfringement to Baxter. The district court held that Baxter's product did not literally infringe the '176 claims because Baxter did not propose a sevoflurane product with more than 131 ppm

water. Reasoning that disclosure to the USPTO of the prior sale of sevoflurane by Abbot surrendered the subject matter of the sale, the district court found no infringement under the doctrine of equivalents. Based on prosecution history estoppel, therefore, the district court declined to address infringement under the doctrine of equivalents. Abbott appealed to this court, which has exclusive jurisdiction. 28 U.S.C. § 1295(a)(1) (2000).

II.

Claim construction is a matter of law, which this court reviews without deference. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1456 [46 USPQ2d 1169] (Fed. Cir. 1998) (en banc). This court reviews *de novo* all grants of summary judgment by a district court, drawing any reasonable inferences in favor of the nonmovant. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255 (1986); *Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1353 [47 USPQ2d 1705] (Fed. Cir. 1998).

Effective Amount

The primary issue on appeal is the district court's construction of the claim term "effective amount." At the outset, this court notes that the term "effective amount" has a customary usage. Under this usage, the term would mean "the amount of Lewis acid inhibitor that will prevent the degradation of sevoflurane by a Lewis acid." *See Minn. Mining & Mfg. Co. v. Chemque, Inc.*, 303 F.3d 1294, 1299, 1304 [64 USPQ2d 1270] (Fed. Cir. 2002) (affirming the district court's construction of the claim term "effective amount" to mean "a sufficient amount of the specified component to form an encapsulant having the specified properties under the specified conditions, if any.").

Moreover, the '176 specification teaches that an effective amount of any given Lewis acid inhibitor will vary depending upon the conditions to which sevoflurane is subjected. The term "effective amount" is broadly described in the "Summary of the Invention" as an "effective stabilizing amount of Lewis Acid inhibitor" that "prevents the degradation of the fluoroether compound by a Lewis acid." '176 patent, col. 2, ll. 60-65. The specification teaches that degradation of fluoroether anesthetics, such as sevoflurane, vary depending upon the environment of the anesthetic. For example, the amount of Lewis acid inhibitor needed to prevent degradation of sevoflurane increases with increasing temperature. '176 patent, col. 8, ll. 18-20. Similarly, Type III glass, normally inert to sevoflurane, activates in some anhydrous, acidic environments. Activated glass exposes sevoflurane to Lewis acid reactive sites. '176 patent, col. 5, ll. 48-54. Examples 5-7 in the '176 patent inhibit degradation of sevoflurane by activated Type III glass by adding 400 ppm water.

Type I glass, chemically distinct from Type III glass, activates in the presence of 50 mg aluminum oxide, a known Lewis acid. Again, the specification addresses this degradation hazard by adding 260 ppm water. '176 patent, col. 5, ll. 55-col. 6, l. 16; Figure 1. The '176 patent thus explains that many different factors interact to dictate an "effective amount" of Lewis acid inhibitor to stabilize sevoflurane in a specific environment. Because the patentee did not deviate from the accustomed meaning of the disputed claim term, the term "effective amount" is construed in view of its ordinary and customary meaning. *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 [62 USPQ2d 1658] (Fed. Cir. 2002) (stating that claim terms are afforded a "heavy presumption" that their ordinary and customary meanings apply). At a minimum, the '176 patent provides support for defining an "effective amount" of inhibitor to be the amount of Lewis acid inhibitor needed to stabilize sevoflurane housed in a particular glass vessel under a given set of environmental conditions. Thus, the specification supports the concept that the amount of Lewis acid inhibitor depends on many environmental considerations.

[1] These principles also explain the relevance of the prior sale disclosed in the IDS. Particularly because the prior sale involved sevoflurane in a specific glass container with a water content of no more than 131 ppm, Abbott's disclosure to the USPTO did not disavow or relinquish all water concentrations below 131 ppm in other conditions. In the context of this invention, Abbott's disclosure did not expressly disavow claim scope. *See York Prods., Inc. v. Cent. Tractor Farm & Family Ctr.*, 99 F.3d 1568, 1575-76 [40 USPQ2d 1619] (Fed. Cir. 1996) ("[U]nless altering claim language to escape an examiner rejection, a patent applicant only limits claims during prosecution by clearly disavowing claim coverage."). In *York*, for example, this court found no surrender of claim scope be-

cause the file history of the asserted patent did not contain "a single statement that the inventors conceded any coverage based on the [the prior art]," and the "mere invocation" of prior art does not necessitate limiting claim scope. *Id.* Indeed, this court recently reiterated the rule that only a clear disavowal of subject matter divests claims of broader scope. *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313 [63 USPQ2d 1374] (Fed. Cir. 2002). In *Teleflex*, this court stated: "[W]e conclude that claim terms take on their ordinary and accustomed meanings unless the patentee demonstrated an intent to deviate from the ordinary and accustomed meaning of a claim term by redefining the term or by characterizing the invention in the intrinsic record using words or expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope." *Id.* at 1324.

In this case, the district court incorrectly limited the term an "effective amount" of water to 131 ppm, despite the absence of a clear disavowal of water at lower amounts. Simply disclosing a previous sale of sevoflurane to the USPTO, without saying or doing anything more, does not disavow or relinquish all water concentrations below 131 ppm. As the patent itself discloses, the effective amount of Lewis acid inhibitor depends on the specific storage conditions of the sevoflurane. Moreover, mere submission of an IDS to the USPTO does not constitute the patent applicant's admission that any reference in the IDS is material prior art. According to Patent Office rules, "[t]he filing of an information disclosure statement shall not be construed to be an admission that the information cited in the statement is, or is considered to be, material to the patentability defined in § 1.56(b)." 37 C.F.R. § 1.97(h) (2000). While valid prior art may be created by the admissions of a party, these admissions are generally characterized by statements made during prosecution describing certain work as "prior art." *See In re Nomiya*, 509 F.2d 566, 571 n.5 [184 USPQ 607] (CCPA 1975); *In re Fout*, 675 F.2d 297, 300-01 [213 USPQ 532] (CCPA 1982). Under certain circumstances, even an express representation that a reference cited in an IDS is prior art to pending claims is not sufficient to create prior art by admission. *Riverwood Int'l Corp. v. R.A. Jones & Co.*, 324 F.3d 1346 [66 USPQ2d 1331] (Fed. Cir. 2003). Thus, with the mere listing of references in an IDS, the applicant has admitted no more than that references in the disclosure may be material to prosecution of the pending claims. 37 C.F.R. § 1.56(a) (2000); *see A.B. Dick Co. v. Burroughs Corp.*, 798 F.2d 1392 [230 USPQ 849] (Fed. Cir. 1986).

Although Abbott sold sevoflurane having water content levels of no more than 131 ppm several years before filing the '176 patent application, Abbott made no express representations about the relevance of these prior sales to the claims. Moreover, the examiner did not reject the claims over the disclosed prior sales of sevoflurane. The mere disclosure of potentially material art to the USPTO does not automatically limit the claimed invention. As noted, the examiner did not consider the sale relevant and the applicant did not distinguish the claims over the disclosed sale. Thus, this court concludes that the district court incorrectly relied on the IDS disclosure to limit the term "effective amount."

[2] In reaching this conclusion, this court notes three instances in the specification where the applicant states an "effective amount" of water ranges from about 0.0150% w/w (150 ppm) to 0.14% w/w (saturation level). '176 patent, col. 4, ll. 32-36; 43-47; 55-58. Contrary to the district court's characterization, these references are not part of the "Summary of the Invention." Instead, these column 4 references fall within the "Detailed Description of the Invention." Thus, these references refer to the preferred embodiments of the invention. Because these references refer only to narrow preferred embodiments and not the invention as a whole, the specification passages do not support the limitation imported into the claims by the district court. The specification simply does not indicate that Abbott restricted its claims to the preferred embodiments. Instead, the specification refers to the water content in these preferred embodiments as amounts that "can be used" or "is believed to be" an appropriate Lewis acid inhibitor. These descriptions in the specification are far from an express disavowal of other effective amounts.

This court interprets patent claims in light of the specification, but this axiom "does not mean that everything expressed in the specification must be read into all the claims." *Teleflex*, 299 F.3d at 1326. "Claims are not necessarily and not usually limited in scope simply to the preferred embodiment." *R.F. Del. v.*

Pac. Keystone Techs., Inc., 326 F.3d 1255, 1263 [66 USPQ2d 1593] (Fed. Cir. 2003). Thus, the specification does not require the claims to be limited to the preferred embodiments. This court declines to so limit the claims in this regard.

Neither does the prosecution history of the '176 patent limit the disputed claim terms. Early in the prosecution, the examiner cited U.S. Patent No. 4,080,389 (issued to Moilliet) as anticipating the subject claims under 35 U.S.C. § 102. Moilliet discloses a fluoroether anesthetic composition containing water vapor. In response to this rejection, Abbott noted that Moilliet "merely indicates that water vapor may be present in the disclosed anesthetic composition ... without specifying the amount of water present in the composition." At no time during this proceeding did Abbott reference the examples in its specification as the only specified water amounts that are "effective" to inhibit Lewis acids. In fact, Abbott never expressly represented that a particular concentration range of Lewis acid inhibitor was critical to distinguishing its claimed invention over Moilliet. Rather, Abbott overcame Moilliet by simply differentiating the trace amounts of water vapor taught in that reference from the claimed amount of water effective as a Lewis acid inhibitor in sevoflurane. At best, Abbott disavowed trace amounts of water as being effective in stabilizing sevoflurane. Thus, this prosecution history does not support limits on the terms "effective amount" or "amount sufficient."

Markush Grouping of Lewis Acids

Asserted claims 1 and 6 recite a list of Lewis acid inhibitors presented in the form of a Markush group. Citing *KJC Corp. v. Kinetic Concepts, Inc.*, 223 F.3d 1351, 1356 [55 USPQ2d 1835] (Fed. Cir. 2000), Abbott argues that the recitation of "a" Lewis acid inhibitor in claims 1 and 6 is understood to mean that "more than one inhibitor would still fall within the claim boundaries." In arguing this construction, Abbott does not account for the Markush groups in claims 1 and 6.

A Markush group is a listing of specified alternatives of a group in a patent claim, typically expressed in the form: a member selected from the group consisting of A, B, and C. Therefore, "if 'wherein R is a material selected from the group consisting of A, B, C and D" is a proper limitation then 'wherein R is A, B, C or D' shall also be considered proper." *In re Harnisch*, 631 F.2d 716, 724 [206 USPQ 300] (CCPA 1980) (containing an Appendix describing Patent Office practice); *see Manual of Patent Examining Procedure (MPEP)* § 2173.05(H) (8th ed. 2001); *see also* Robert C. Faber, *Landis on Mechanics of Patent Claim Drafting*, § 50, 5A, VI-5-6 (4th ed. 2002) ("A Markush group is a sort of homemade generic expression covering a group of two or more different materials (elements, radicals, compounds, etc.), mechanical elements, or process steps, any one of which would work in the combination claimed."). It is well known that "members of the Markush group are ... alternatively usable for the purposes of the invention." *In re Driscoll*, 562 F.2d 1245, 1249 [195 USPQ 434] (CCPA, 1977). Moreover, "[a] Markush group, incorporated in a claim, should be 'closed,' i.e. it must be characterized with the transition phrase 'consisting of,' rather than 'comprising' or 'including.' " Stephen A. Becker, *Patent Applications Handbook* § 2:17 (9th ed. 2000). Thus, "members of the Markush group are used singly." *See Meeting Held to Promote Uniform Practice In Chemical Divisions*, 28 J. Pat. & Trademark Off. Soc'y 849, 852 (1946) (listing practices approved by the primary examiners of the USPTO's chemical group).

In *KJC Corp.*, this court stated that "an indefinite article 'a' or 'an' in patent parlance carries the meaning of 'one or more' in open-ended claims containing the transitional phrase 'comprising.' " *KJC Corp.*, 223 F.3d at 1356. However, such an indefinite article used in conjunction with a Markush grouping does not receive such latitude because a proper Markush group is limited by the closed language term "consisting of." *See Mannesmann Demag Corp. v. Engineered Metal Prods. Co.*, 793 F.2d 1279, 1282 [230 USPQ 45] (Fed. Cir. 1986) (confirming that the phrase "consisting of" appearing in a clause of a claim specifically limits only the element set forth in that clause). Therefore, although "a" without more generally could mean one or more in an open-ended patent claim, "a" with "consisting of" in this case indicates only one member of a Markush group. *See KJC Corp.*, 223 F.3d at 1356. If a patentee desires mixtures or combinations of the members of the Markush group, the patentee would need to add qualifying language while drafting the claim. *See Meeting Held to Promote Uniform Practice In*

Chemical Divisions, *supra*, at 852 (citing examples of qualifying language such as: "and mixtures thereof" and "at least one member of the group"). Thus, without expressly indicating the selection of multiple members of a Markush grouping, a patentee does not claim anything other than the plain reading of the closed claim language.

[3] Abbott's claims do not have such qualifying language. Because the claims do not clearly embrace more than one member of the Markush group, only one Lewis acid inhibitor falls within the claim scope. Thus, the plain meaning of asserted claims 1 and 6 limits them to a single Lewis acid inhibitor selected from the recited Markush group, and present in an amount effective to prevent degradation of sevoflurane by Lewis acids.

The file history of the '176 patent supports this analysis. Abbott amended the '176 patent claims during prosecution. Independent claim 1, as initially filed, recited "a fluoroether compound having an alpha fluoroether moiety having added thereto an effective amount of a Lewis acid inhibitor." Independent claim 6, as originally filed, recited "adding to the fluoroether compound an effective stabilizing amount of a Lewis acid inhibitor to prevent the degradation of the fluoroether compound by the Lewis acid." After amendment, claims 1 and 6 recite a specific inhalant anesthetic, sevoflurane, and specific Lewis acids inhibitors. '176 patent, col. 11, ll. 22-29. In an Interview Summary, the examiner stated that he reached agreement with applicants "to narrow the claims to include a specific inhalant anesthetic and specific Lewis acid inhibitors in order to avoid 112 issues." The examiner's reasons for allowance made the same observations.

Thus, the patent applicant added the Markush group reciting specific Lewis acid inhibitors to comply with 35 U.S.C. § 112 and gain allowance. In doing so, Abbott disclaimed any coverage for Lewis acid inhibitors other than the six listed members of the Markush groups in issued claims 1 and 6. Consequently, the file history shows that the applicant expressly defined the claim term "Lewis acid inhibitor" as a member of the recited Markush group. Thus, claims 1 and 6 embrace a Lewis acid inhibitor selected from those inhibitors recited in the Markush group.

III.

[4] This court need not construe the claims of the '176 patent as requiring more than 131 ppm of water to preserve their validity under 35 U.S.C. § 102(b) in view of Abbott's prior sale of sevoflurane. In the first place, the district court expressly declined to determine the validity of the '176 patent claims. The district judge noted that the parties did not raise the issue of validity and also observed that the " 'clear and convincing evidence' required to invalidate a patent has not yet been shown here." *Abbott*, 2002 WL 449007, at *6. Despite this observation, the district court concluded that "the only way to maintain the validity of the '176 patent, then, would be to interpret the terms 'sufficient' or 'effective' amount as requiring at least 131 ppm of water." In effect, the district court reached out to make a validity determination, despite the lack of invalidating evidence.

It is sometimes difficult to balance a patentee's broad claim reading against an assertion that the claims at some indefinite breadth may be invalid. *See Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1384 [58 USPQ2d 1286] (Fed. Cir. 2001). In this case, however, the district court did not have evidence that Abbott's sale of sevoflurane constituted prior art to the claimed invention. The record did not show whether the previously sold sevoflurane contained an amount of water capable of effectively inhibiting Lewis acids under those unique storage conditions. The record does contain Abbott's assertion that the amount of water in the previously sold sevoflurane compositions was ineffective for preventing degradation of sevoflurane in glass bottles. Abbott contends that this problem provided the impetus for its studies that ultimately lead to the '176 patent. As noted, Baxter does not adequately address whether the prior sale is truly material prior art to the claimed invention. Rather, Baxter incorrectly assumes that disclosure of a reference to the USPTO is an admission that the reference is material prior art.

The district court properly noted that invalidity must be proven by clear and convincing evidence. *Tate Access Floors, Inc. v. Interface Architectural Res.*, 279 F.3d 1357, 1367 [61 USPQ2d 1647] (Fed. Cir. 2002). Without such evidence, and without the issue of validity properly presented for the record, the district court erred by giving the claim term "effec-

tive amount" a narrow reading to preserve its validity. On remand, if the issue of validity is properly presented, the court will have the opportunity to determine whether this prior sale affects the validity of the claims.

IV.

The district court granted summary judgment of noninfringement based on its claim construction restricting water as a Lewis acid inhibitor only when present in sevoflurane at an amount greater than 131 ppm. The district court determined that Baxter's proposed sevofluorane composition contains not more than 130 ppm, and therefore, does not literally infringe the '176 patent. Because the district court's construction is flawed, this court remands for further consideration of literal infringement in view of the claim construction discussed herein.

Abbott argues that Baxter's sevoflurane composition having less than 131 ppm water in a vessel possessing an epoxyphenolic resin liner literally infringes the '176 claims under its proffered construction. Abbott notes that Baxter's combination of two Lewis acid inhibitors, even if each is individually present at an ineffective amount, results in an amount of Lewis acid inhibitor capable of effectively inhibiting sevoflurane degradation by Lewis acids. This combination, according to Abbott, satisfies the claim element of "a Lewis acid inhibitor" and therefore, it was error for the district court to decide infringement on summary judgment when this issue of material fact was still in dispute. Abbott does not properly consider the constraints placed on claims 1 and 6 by the introduction of the Markush group during prosecution, as discussed above. To prove literal infringement of these claims on remand, Abbott must show a species selected from the members of the recited Markush group is present in Baxter's sevoflurane composition in an amount effective to function as a Lewis acid inhibitor.

Despite a listing of various suitable container materials – glass, plastic, and steel – in column 5, the district court "found no mention in the '176 patent that the type of container would make a difference" in the amount of Lewis acid inhibitor required in a given packaging. To the contrary, the specification clarifies that, at least with respect to glass containers, the amount of Lewis acid inhibitor varies depending upon the type of glass and other characteristics and conditions of the container. Moreover, the specification need not teach that which is already known to artisans of ordinary skill. Therefore, on remand, the court will have the opportunity to develop a record on this point as well.

Abbott also contends the district court erred by barring it from asserting infringement under the doctrine of equivalents. The district court determined that the doctrine of equivalents was not available to Abbott "because of the prior art sale," citing *Wilson Sporting Goods Co. v. David Geoffrey & Associates*, 904 F.2d 677, 684 [14 USPQ2d 1942] (Fed. Cir. 1990) (stating "a patentee should not be able to obtain, under the doctrine of equivalents, coverage which he could not lawfully have obtained from the PTO by literal claims"). Likewise, this court has opined "a patentee cannot narrowly claim an invention to avoid prosecution scrutiny by the PTO, and then, after patent issuance, use the doctrine of equivalents to establish infringement because the specification discloses equivalents." *Johnson & Johnston Assocs. Inc. v. R.E. Serv. Co.*, 285 F.3d 1046, 1054 [62 USPQ2d 1225] (Fed. Cir. 2002) (en banc). It may be argued that requiring a patentee to claim subject matter that the patent drafter reasonably could have anticipated and described during the application process serves to "enhance[] the notice function of claims." *Id.* at 1056-57. The district court declined to consider the applicability of infringement by equivalents in view of *Festo*, which was under consideration by the Supreme Court at the time the district court's decision was rendered. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 122 S. Ct. 1831 [62 USPQ2d 1705] (2002). On remand, Abbott will have the opportunity to establish infringement by equivalents in view of this court's claim construction. The effect of the decisions in *Wilson Sporting Goods*, *Johnson & Johnston*, and *Festo* on infringement of the '176 patent via equivalents should be evaluated by the district court. In sum, this court vacates the district court's decision, and remands for further consideration of infringement consistent with this opinion.

COSTS

Each party shall bear its own costs.

VACATED and REMANDED

Exhibit 2

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RESEARCH PAPER *Multiple Sclerosis* 2008; **00**: 1–8

Glatiramer acetate after induction therapy with mitoxantrone in relapsing multiple sclerosis

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Forty relapsing multiple sclerosis patients with 1–15 gadolinium (Gd)-enhancing lesions on screening brain magnetic resonance imaging (MRI) and Expanded Disability Status Scale (EDSS) scores 0–6.5 were randomized to receive short-term induction therapy with mitoxantrone (three monthly 12 mg/m^2 infusions) followed by 12 months of daily glatiramer acetate (GA) therapy 20 mg/day subcutaneously for a total of 15 months (M-GA, $n = 21$) or daily GA 20 mg/day for 15 months (GA, $n = 19$). MRI scans were performed at months 6, 9, 12 and 15. The primary measure of outcome was the incidence of adverse events; secondary measures included number of Gd-enhanced lesions, confirmed relapses and EDSS changes. Except age, baseline demographic characteristics were well matched in both treatment arms. Both treatments were safe and well tolerated. M-GA induction produced an 89% greater reduction (relative risk (RR) = 0.11, 95% confidence interval (CI): 0.04–0.36, $p = 0.0001$) in the number of Gd-enhancing lesions at months 6 and 9 and a 70% reduction (RR = 0.30, 95% CI: 0.11–0.86, $p = 0.0147$) at months 12 and 15 versus GA alone. Mean relapse rates were 0.16 and 0.32 in the M-GA and GA groups, respectively. Short-term immunosuppression with mitoxantrone followed by daily GA for up to 15 months was found to be safe and effective, with an early and sustained decrease in MRI disease activity. *Multiple Sclerosis* 2008; **00**: 1–8. http://msj.sagepub.com

Key words: multiple sclerosis; immunology; de-myelinating disease; combination therapy; mitoxantrone; glatiramer acetate; induction therapy

Introduction

The immunomodulator, glatiramer acetate (GA; Copaxone®, Teva Neuroscience, Kansas City, MO), is approved for the treatment of relapsing–remitting multiple sclerosis (RRMS). Several immunomodulatory mechanisms have been proposed to account for GA efficacy in multiple sclerosis (MS). Although the exact mechanism is not known, there is good evidence that the benefit of GA is mediated through memory T lymphocytes involved in regulation of immunity, with no evidence of systemic immunosuppression [1–6]. GA also affects antigen presenting cells and influences humoral immunity, increasing the levels of serum GA-reactive antibodies [7–10].

GA significantly reduces inflammation-related disease activity such as relapses and magnetic resonance imaging (MRI) lesion development and slows accumulation of disability as measured by the Expanded Disability Status Scale (EDSS) [11,12]; but like other first-line immunological therapies for MS, the efficacy of GA is only partial. Combining therapies with different modes of action may improve efficacy; however, certain combinations,

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such as natalizumab and interferon β-1a may also increase the risk of unanticipated side effects [13]. The benefits of combination therapy without sacrificing safety might be derived by utilizing brief immunosuppressive therapy combined with a non-immunosuppressive agent, such as GA. Moreover, induction of immunosuppression may accelerate GA efficacy by rapidly ablating autoaggressive T cells, thereby reducing competition with emerging protective GA-reactive T cells.

Mitoxantrone, an antineoplastic agent marketed in the US since 1989, has also been approved in the US for worsening forms of RRMS and for progressive relapsing MS (PRMS) or secondary progressive MS (SPMS) [14]. Mitoxantrone has shown efficacy in reducing relapse rates and the number of gadolinium (Gd)-enhancing lesions on MRI in MS patients [15–17]. Cardiac toxicity is a potential serious adverse effect of mitoxantrone treatment and is dose-related. The recommended maximal cumulative life dose should not exceed 140 mg/m^2 (see [14]). Secondary acute myelogenous leukemia (AML) has been reported in MS patients treated with mitoxantrone with a risk of 0.25% (2/802) [14]. Additional adverse events found to be significantly more frequent in MS patients treated with mitoxantrone in two studies include: nausea, alopecia, urinary tract infections and menstrual disorders, including amenorrhea [14]. Thus, although highly effective, it must be used sparingly over the course of a disease that lasts a lifetime. Brief use of mitoxantrone followed by occasional pulse doses in the context of combination therapy may minimize safety risks and extend the usefulness of this therapy over a longer course.

This study, in RRMS patients with active disease, was conducted to determine whether treatment with GA after brief immunosuppression with mitoxantrone is well tolerated and safe, as determined by clinical, laboratory and MRI parameters. We also evaluated whether short-term immunosuppression followed by chronic GA therapy provides superior efficacy compared with exposure to GA alone.

Methods

Patients

Inclusion criteria

Males and females between 18 and 55 years of age with clinically definite MS as determined by the McDonald criteria [18] with a relapsing disease course and EDSS score between 0 and 6.5 inclusive were eligible. Patients must have had active disease, as indicated by at least 1, but not more than 15, Gd-enhancing lesions on a screening brain MRI.

Exclusion criteria

Exclusion criteria are as follows: previous treatment with GA or mitoxantrone; treatment with intravenous immunoglobulins (IVIg) or interferons within 4 weeks of the screening visit; treatment with azathioprine or methotrexate within 6 months of screening visit; treatment with intravenous (IV) or oral steroids within the 28 days before initial MRI; any prior use of cyclophosphamide, cladribine, anthracenediones, anthracycline or receipt of total lymphoid irradiation (TLI) or mediastinal radiotherapy; left ventricular ejection fraction (LVEF) less than 50%; need for a catheter or Foley catheter; known systemic or neurological disease that might confound evaluation of study results (e.g. amyotrophic lateral sclerosis, Lyme disease); or immune condition or medical condition precluding the use of either study drug. Also, patients were excluded if screening blood tests were abnormal, i.e. exceeded any of the following limits: alanine transaminase (ALT) or aspartate transaminase (AST) twice the upper limit of normal (test may be repeated once), baseline absolute neutrophil counts of less than 1.5 × 10^3/μl, absolute white lymphocyte count less than 2.3 × 10^3/μl, platelet count less than 80 × 10^3/μl, creatinine greater than 1.5 mg/dl or prothrombin time over 50% of the upper limit of normal. Female patients were not pregnant or lactating and had a negative screening pregnancy test; both male and female patients were required to use contraception deemed reliable by the investigator.

Study design

Six North American centers enrolled patients in this randomized, single-blind, two-arm study. The study protocol was approved by each participating center's Institutional Review Board (IRB) and all patients provided written, informed consent before participating. Patients were randomized at each center through a standard randomization procedure developed by the study statistician and administered by a dispensing pharmacist at each site (where available) or by the sponsor. The randomization scheme included blocking within center to insure relative balance of the number of patients per site and by treatment. Patient allocation to treatment groups employed a one-to-one assignment ratio. Eligible patients randomized to undergo mitoxantrone induction therapy (M-GA arm) received three doses of mitoxantrone 12 mg/m^2 given as a short (5–15 minutes) IV infusion at

months 0, 1 and 2, followed by a 2-week washout period, then began daily subcutaneous injections of GA 20 mg. Treatment with GA continued for approximately 12.5 months, for a total treatment period of 15 months. Patients randomized to GA alone (GA arm) received daily injections of GA 20 mg over the entire 15-month study.

Patients were evaluated for safety before and after each mitoxantrone treatment (M-GA group) and efficacy assessments occurred every 3 months during the GA treatment phase (both groups). Patients receiving mitoxantrone could receive a prophylactic antiemetic at the discretion of the investigator. Symptomatic MS treatments such as anticholinergic and spasmolytic drugs were allowed as required. Relapses were treated with a 3-day course of IV methylprednisolone (1000 mg/day). Concomitant treatment with any investigational drug, other immunomodulating therapies, chemotherapy, immunosuppressant or steroids (e.g. chronic oral corticosteroids or IV methylprednisolone other than for treatment for relapse) was not allowed. Use of a statin for vascular disease was permitted; however, statin use for the purpose of treating MS was not allowed.

Safety and tolerability assessments

Table 1 shows the schedule of measures used to evaluate the primary endpoint of safety and tolerability in this study. All patients underwent safety evaluations at the screening visit. The M-GA group repeated blood and lab chemistries at the baseline visit, and prior to and after each mitoxantrone infusion. Immunosuppression and drug toxicity were measured by complete blood count (CBC) with the following differentials: absolute lymphocyte, absolute neutrophil and platelet counts; levels of AST, ALT, alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), creatinine and glucose; electrolyte panel; and urinalysis. Patients were assessed within 72 h prior to the mitoxantrone administration and drug infusion could occur only if white blood cell (WBC) counts indicated safe continuation, as determined by the investigator. Post-mitoxantrone follow-up visits occurred within 14 ± 4 days after infusion. The date of the last mitoxantrone dose marked the start of the 2-week washout period before beginning GA.

Cardiac toxicity was assessed by multiple gated acquisition (MUGA) for LVEF performed at the first pre-mitoxantrone infusion visit, 2 weeks after the last mitoxantrone infusion and at month 15.

Efficacy assessments

Secondary endpoints included efficacy, as assessed by drug effects on MRI markers of inflammation, i.e. the number of Gd-enhancing lesions on T1-weighted images on brain MRI. Additional MRI metrics are reported elsewhere [19]. MRI scans were performed at the screening visit and at months 6, 9, 12 and 15. Outcomes of interest were differences in the number of Gd-enhancing lesions between treatment arms at months 12 and 15 and at months 6 and 9. Scans were performed with a 1.5 T field strength scanner using the same standardized sequences for the duration of the study. Gadolinium contrast agent was given at 0.1 mmol/kg (0.2 ml/kg), IV administration over 1 min, followed by a post-injection delay of 5 min before scanning. Gd-enhancing lesions were counted on pre- and post-gadolinium axial T1-weighted scans obtained using a fast field echo sequence with a Gaussian, off-resonance magnetization transfer pulse to suppress the background signal (time of repetition (TR) = 30 ms, time of echo (TE) = 11 ms, flip angle 30°, slice thickness 3 mm and 256×256 matrix). Blinded image analysis was performed at the Image Analysis Center at the Montreal Neurological Institute and NeuroRx Research, Montreal, Canada.

Additional efficacy measures included relapse rate (relapse was defined as the appearance or reappearance of at least one neurological abnormality persisting for at least 48 h and occurring at least 30 days after the onset of a previously confirmed relapse), proportion of relapse-free patients and time to first relapse. Patients were evaluated by a treating physician within 7 days of a suspected relapse. EDSS evaluations were performed by an examining physician who remained blinded to the treatment assignment. Confirmed disability accumulation was defined as a change in EDSS score of at least 1.0 point for patients with baseline EDSS score at most 5.0, or a 0.5 point change in EDSS score for patients with EDSS 5.5–6.5, sustained for at least 3 months. Also measured was change in MS Functional Composite (MSFC) score at baseline and at each follow-up visit (patients were given three practice exams during the screening visit, before the baseline measure was taken).

Patients and site personnel were not blinded to treatment assignment; however, examining neurologists and those who administered the MSFC were blinded to patients' therapy. Patients and treating physicians were instructed of the importance of not discussing safety issues or treatment assignment with the examining physician or the MSFC examiner.

A treating physician was responsible for patient monitoring, adverse event assessment, physical exams and identification of possible relapses.

Table 1 Study design: safety assessment and drug administration schedule

Visits	Pretreatment	Treatment period													
	Scrn and Randomization	M0			M1			M2			M3	M6	M9	M12	M15
Procedures		0.1 (BL)	0.2	0.3	1.1	1.2	1.3	2.1	2.2	2.3					
Informed Consent	•														
Med History/MS History	•														
Inclusion/Exclusion Criteria	•														
Physical Exam	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦
	×														×
Concomitant Medications	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦
	×		×								×	×	×	×	×
Vital Signs	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦
	×		×								×	×	×	×	×
CXR, EKG, Coagulation	♦														
	×														
MUGA		♦								♦					♦
LAB Chemistry	♦	♦		♦	♦		♦	♦		♦	♦	♦	♦	♦	♦
	×		×								×	×	×	×	×
LAB Hematology	♦	♦		♦	♦		♦	♦		♦	♦	♦	♦	♦	♦
	×		×								×	×	×	×	×
LAB hCG	♦	♦			♦			♦							♦
	×														×
Urinalysis	♦	♦		♦	♦		♦	♦		♦	♦	♦	♦	♦	♦
	×		×								×	×	×	×	×
Adverse Events		♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦	♦
			×								×	×	×	×	×
Mitoxantrone Administration			♦			♦			♦						
GA Administration										♦	♦	♦	♦	♦	♦
			×	×	×	×	×	×	×	×	×	×	×	×	×

♦ = M-GA cohort; × = GA cohort.

Statistical analyses

Statistical power determination was based on expected differences between study arms in total number of enhancing lesions at months 12 and 15. For a two-sided α-level of 5% and a treatment effect of 90% in the M-GA group, a total of 20 patients per group were required for a power of 90.1%.

All analyses used intention-to-treat (ITT) principles. Patient characteristics at baseline were examined using a two-sample t-test or Mann–Whitney test (continuous variables) when appropriate, and by a χ^2 test or Fisher's exact test (categorical variables) when appropriate. Adverse event incidence and frequency were evaluated by treatment group, severity and relationship to study drug. For laboratory testing, frequency counts and data outside the normal range at each scheduled visit, and shift analysis from baseline to last observed value, were recorded.

The number of Gd-enhancing lesions was compared between treatment groups using a Poisson regression (SAS PROC GenMod) analysis with the number of Gd-enhancing lesions at the screening visit as a covariate. Treatment and center effects were used in the model if the center-by-treatment interaction term was found to be significant. The composite numbers of enhancing lesions counted in scans taken at months 12 and 15, and in scans taken at months 6 and 9 were compared between treatment groups. Type 1 error adjustment for multiple comparisons was made according to Hochberg's step-up modification to the Bonferroni method [20]. Relapse rate was recorded as the number of relapses over the 15-month period, and was analyzed using Poisson regression with baseline EDSS score, age and gender included in the model as covariates. The change in EDSS score from baseline to each visit was analyzed by applying a repeated measures analysis of covariance (SAS mixed procedure). The model included the following fixed effects: treatment group, week in trial and treatment-by-week interaction. The test for a significant treatment effect was based on the joint statistical significance of the treatment effect and the treatment-by-week interaction.

Results

Patients

Of the 93 patients screened, 43 were randomized and 3 patients discontinued before receiving the

Table 2 Patient characteristics at baseline

	M-GA ($n = 21$)	GA ($n = 19$)	All ($n = 40$)	p-value
Age (years; mean ± SD)	33.7 ± 8.3	41.2 ± 9.8	37.2 ± 9.7	0.0126
Females	71%	53%	63%	0.3284
Years since diagnosis (mean ± SD)	4.0 ± 5.2	2.8 ± 4.4	3.5 ± 4.8	0.4355
Number of Gd-enhancing lesions (mean ± SD)	3.8 ± 3.9	3.7 ± 4.1	3.8 ± 4.0	0.9217
EDSS (mean ± SD)	2.3 ± 1.0	2.3 ± 1.3	2.4 ± 1.2	0.9973
Years since last relapse (mean ± SD)	1.0 ± 2.1	0.6 ± 0.4	0.8 ± 1.5	0.3684
MSFC score (mean ± SD)	0.24 ± 5.9	0.71 ± 5.7	0.46 ± 5.7	0.7986

study drug; therefore, a total of 40 evaluable patients comprised the study population (M-GA $n = 21$; GA $n = 19$). The majority of screen failures (54%) occurred because patients did not meet MRI inclusion criteria. The first patient in the study was screened in June 2003 and the last patient completed the month 15 visit in March 2006. Two patients discontinued the study: one from the M-GA group (lost to follow-up) and one from the GA group (patient's decision to terminate); both patients are included in ITT analyses. Mean, disease durations, EDSS scores and numbers of Gd-enhancing lesions were matched in the two treatment arms (Table 2). The mean cumulative mitoxantrone dose was 36 mg/m^2.

Treatment was generally well tolerated; no patient withdrew from the study owing to an adverse event or to lack of tolerability. One serious adverse event occurred during the study: a 47-year-old female in the GA group required hospitalization for pyelonephritis, which was not considered related to the study drug.

Primary endpoint

The most common adverse events with mitoxantrone were infections: 17 M-GA patients (81%) reported infections, including influenza (9.5%), nasopharyngitis (23.8%), sinusitis (19.0%), upper respiratory tract infection (38.1%) and urinary tract infection (19.0%) (Table 3). Six patients (31.6%) in the GA group also experienced infections, including upper respiratory infection (26.3%), nasopharyngitis (10.5%), urinary tract infection (10.5%) and dental caries (5.3%). Amenorrhea occurred in three patients (ages 41, 32 and 28 years) and resolved after completion of mitoxantrone treatment. The most common adverse events associated with GA therapy were injection site reactions, the majority of which involved erythema. Symptoms consistent with an immediate post-injection reaction (IPIR) were reported in both treatment arms (M-GA: hot flush $n = 5$, chest discomfort $n = 3$, dyspnea $n = 1$; GA: chest discomfort $n = 1$, palpitations $n = 3$). Three instances of IPIR were reported for M-GA patients during mitoxantrone treatment and all other instances occurred during GA treatment. All IPIRs resolved without discontinuation of therapy.

Table 3 Safety Outcomes

Adverse event	M-GA ($n = 21$)	GA ($n = 19$)
Infections	81.0%	31.6%
Nausea	66.7%	10.5%
Alopecia	28.6%	0%
Amenorrhea	14.3%	0%
IPIR	42.9%	15.8%
Injection site reactions	47.6%	52.6%

Immunosuppression by mitoxantrone was evident by reductions in WBC, lymphocyte, monocyte, and neutrophil counts measured post-dose, approximately 14 days after each mitoxantrone infusion (Table 4). At baseline WBC counts were 7.79 ± 2.02 × 10^3/μl and after the last dose of mitoxantrone the counts were 3.25 ± 0.86 × 10^3/μl. ANC were 5.17 ± 1.85 × 10^3/μl at baseline and 1.61 ± 0.70 × 10^3/μl at 14 days after mitoxantrone dosing. By the last observation, WBC and differential counts had returned to near-baseline levels and as early as the month 9 visit, 100% of M-GA patients had returned to within the normal ranges for absolute counts of WBCs, lymphocytes, monocytes and neutrophils.

Laboratory assessments (serum creatinine, alkaline phosphatase, gamma glutamyl transferase, ALT, AST, BUN) and urinalysis indicated no significant effect of mitoxantrone (or GA) on liver or kidney function, and vital sign assessments revealed no clinically relevant or persistent adverse effects of either study drug. Similarly, MUGA results indicated no adverse effect of mitoxantrone on LVEF; mean change from baseline in M-GA patients was 1.9 ± 6.1% (baseline mean 59.2%; last observation mean 60.6%, range 47–70%).

Secondary endpoints

At 15 months, the mean (± standard error (SE)) number of enhancing lesions was reduced in the M-GA group from 3.8 ± 0.85 at baseline to 0.47 ± 0.37 (–88%), and in the GA group from 3.7 ± 0.95 to 1.2 ± 0.90 (–66%). The relative risk (RR) of Gd-enhancing

Table 4 WBC and differential counts

Analyte	M-GA (n = 21)	Count
WBC (×10³/μL); mean ± SD	Baseline	7.79 ± 2.02
	Post-dose	3.25 ± 0.86
	Month 9	6.50 ± 1.26
	Last observation	6.76 ± 1.30
	Change from baseline*	−1.03 ± 1.65
Neutrophil (×10³/μL); mean ± SD	Baseline	5.17 ± 1.85
	Post-dose	1.61 ± 0.70
	Month 9	4.48 ± 1.07
	Last observation	4.56 ± 1.07
	Change from baseline	−0.60 ± 1.52
Lymphocyte (×10³/μL); mean ± SD	Baseline	2.10 ± 0.57
	Post-dose	1.31 ± 0.34
	Month 9	1.47 ± 0.41
	Last observation	1.64 ± 0.42
	Change from baseline	−0.45 ± 0.45
Monocytes (×10³/μL); mean ± SD	Baseline	0.35 ± 0.14
	Post-dose	0.25 ± 0.09
	Month 9	0.36 ± 0.07
	Last observation	0.35 ± 0.12
	Change from baseline	0.01 ± 0.13
Eosinophils (×10³/μL); mean ± SD	Baseline	0.14 ± 0.09
	Post-dose	0.08 ± 0.09
	Month 9	0.15 ± 0.09
	Last observation	0.16 ± 0.08
	Change from baseline	0.02 ± 0.09
Basophils (×10³/μL); mean ± SD	Baseline	0.04 ± 0.02
	Post-dose	0.02 ± 0.01
	Month 9	0.05 ± 0.03
	Last observation	0.04 ± 0.02
	Change from baseline	−0.00 ± 0.03
Platelets (×10³/μL); mean ± SD	Baseline	295.10 ± 63.10
	Post-dose	232.67 ± 62.01
	Month 9	250.45 ± 47.39
	Last observation	258.71 ± 52.73
	Change from baseline	−36.38 ± 37.66

*Change in baseline counts to last observation counts.

lesions in M-GA patients versus GA patients was 0.18 ± 0.09 (95% CI: 0.07–0.47; $p < 0.0001$; see Figure 1). Differences in Gd-enhancing lesions occurred between M-GA and GA at months 6 and 9 (RR = 0.11, 95% CI: 0.04–0.36; $p < 0.0001$) and at months 12 and 15 (RR = 0.30, 95% CI: 0.11–0.86; $p = 0.0147$).

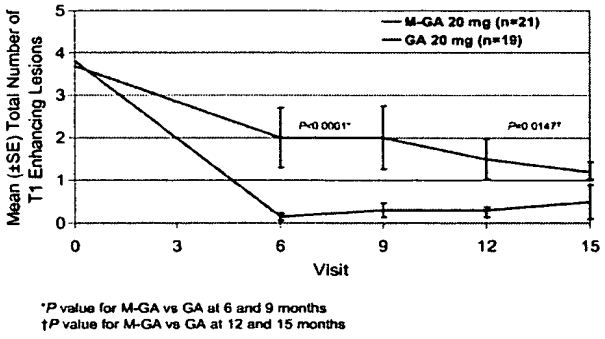

Figure 1 Mean (±SE) total number of T1 Gd-enhancing lesions.

Eight patients experienced a relapse during the study: four relapses were reported in the M-GA group and eight were reported in the GA group (RR = 0.54, 95% CI: 0.16–1.84; $p = 0.31$; see Figure 2) during the 15-month study. There was no difference between groups in mean time to first relapse. Estimated mean times to first relapse were 222 and 247 days in the M-GA and GA treatment groups, respectively ($p = 0.8914$). Mean relapse rates at 15 months were 0.16 ± 0.34 with M-GA and 0.32 ± 0.66 with GA. During the 15-month study, 81% of M-GA patients and 79% of GA patients remained relapse-free.

Small, non-significant and similar changes from mean baseline EDSS scores were noted in both treatment groups over the course of the study. Mean changes in EDSS were −0.18 ± 0.60 and −0.14 ± 0.69 for M-GA and GA patients, respectively. Only one patient in the study (GA treatment arm) experienced confirmed disease progression (EDSS score changed from 3.0 at baseline to 5.0 and 6.0 at the visits in months 12 and 15).

Similarly, small, non-significant improvements from baseline MSFC scores were noted in both treatment groups: −1.5 ± 4.1 in the M-GA arm and −0.24 ± 3.5 in the GA arm.

Discussion

These results suggest short-term immunosuppression with mitoxantrone followed by daily GA 20 mg/day is safe and generally well tolerated, and this regimen prevents Gd-enhancing brain lesions more effectively than the currently approved GA 20 mg/day dose alone. Mitoxantrone quickly ameliorates inflammation, which is reflected by the rapid reduction of enhancing lesions on MRI; in contrast, the anti-inflammatory effects of GA on MRI disease activity, thought to be related to 'bystander suppression' within the central nervous system [3], increased gradually over the course of the study, resulting in a 60% difference between the two treatment arms in the number of Gd-enhancing lesions at 15 months.

In tandem with the reduction of enhancing lesions, patients in both treatment groups experienced low relapse rates. Approximately 80% of all patients, who began the trial with active inflammation as indicated by a mean of 3.8 enhancing lesions before study entry, remained relapse free over the course of the 15-month study.

Changes from baseline and between treatment groups in EDSS scores were not significant, possibly because of the small size and the short duration of the trial. One patient in the GA treatment arm experienced disease progression over the course of the 15-month study. Similarly, small improvements in MSFC scores over the course of the study were not different between study groups.

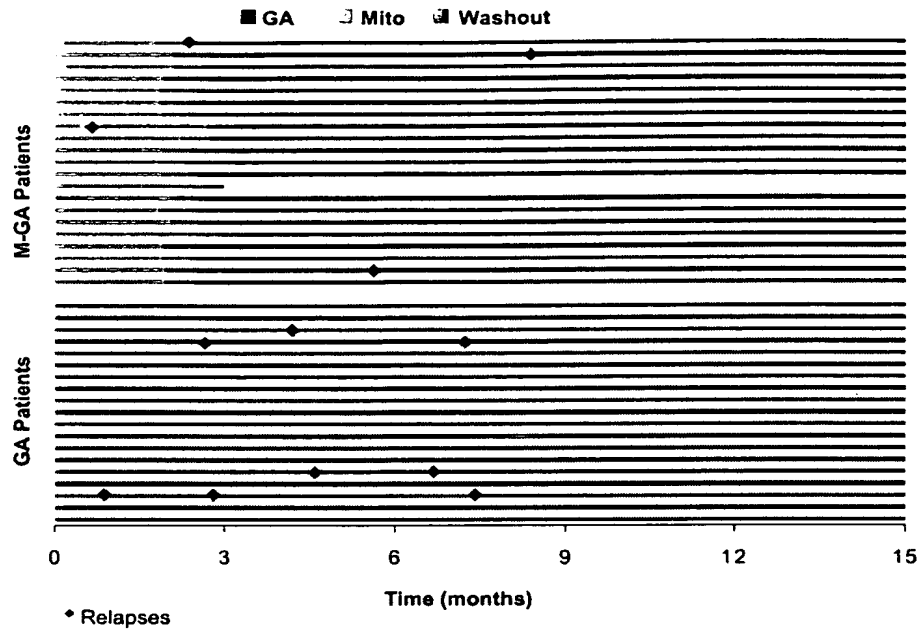

Figure 2 Relapses during the study.

Short-term immunosuppression followed by immunomodulation may improve clinical outcomes while limiting the detrimental adverse events associated with long-term immunosuppressive therapy such as development of progressive multifocal leukoencephalopathy after prolonged treatment with natalizumab [21] or congestive heart failure related to extended treatment with mitoxantrone [14]. The most frequent adverse events in the M-GA group in this study were infections, which is consistent with the known safety profile of mitoxantrone [14–17].

In addition to the increased risk of adverse events, the use of immunosuppressants to suppress inflammation over extended periods may inhibit innate neuroprotective and recovery mechanisms [22]; it has been reported, for example, that cyclophosphamide treatment is deleterious to oligodendrocyte remyelination [23,24]. As evidenced by the reduction in WBC, lymphocytes and neutrophils in this study, general immunosuppression occurred with the three infusions of mitoxantrone; however, by the month 9 clinic visit, WBC and differential counts had returned to within normal ranges, indicating a recovery of immune function. This recovery may facilitate the ability of GA to induce the memory T lymphocytes that mediate its therapeutic effect, and may also be associated with enhancement of innate neuroprotective properties of the immune system, for example, the production of neurotrophic factors and the stimulation of remyelination [3,22,25].

Our results are in accordance with those recently reported in a single-arm study by Ramtahal, *et al.* [26]. Twenty-seven RRMS patients with highly active MS received monthly induction therapy with mitoxantrone for 3–6 months, then combination mitoxantrone-GA for 2 months, followed by daily GA therapy. The mean follow-up time from the start of mitoxantrone was 36 months and the mean duration of GA monotherapy was 22 months. Average annualized relapse rate was reduced 96% following mitoxantrone therapy (from 2.7 in the 2 years before the study to 0.106; $p < 0.001$). Only two relapses were reported while patients received GA; notably, they occurred in two patients who had experienced continuing relapses on GA before participating in the study. (Enhancing lesions on MRI were not evaluated in this study.)

Is there a role for immunosuppressive induction therapy prior to immunomodulator use in the treatment of MS? Unfortunately, results of this study do not reveal how much of the enhanced effect of the M-GA treatment was a result of mitoxantrone alone, given that mitoxantrone may persist in the body for up to 9 months [27], or a result of the combination of mitoxantrone with GA. The addition of a third treatment arm of mitoxantrone alone might have answered this question; however, such a study would have required many more patients. Longer follow-up may show whether the benefits of mitoxantrone induction therapy followed by GA treatment are sustained; to this end, a 45-month extension phase of this study is ongoing.

These results and those of other small studies are encouraging, suggesting that the brief use of an immunosuppressant agent such as mitoxantrone

followed by treatment with GA can lead to improved efficacy in relapsing MS. Reductions in Gd-enhancing lesions and relapse rates in this study are comparable with those reported for some of the newer immunosuppressive agents whose long-term safety profile has still to be determined [13,28]. This type of therapy could be reserved for patients whose first-line therapy is not optimally treating their disease or patients who present with highly active disease and are thought to need more aggressive treatment.

Acknowledgments

The authors acknowledge the assistance of Pippa Loupe, PhD, Teva Neuroscience, Kansas City, Missouri and Sheila Owens, BS, Medical Communication Co., Inc., Doylestown, Pennsylvania in the production of the manuscript.

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Exhibit 3

Supreme Court of the United States
KSR INTERNATIONAL CO., Petitioner,
v.
TELEFLEX INC. et al.
No. 04-1350.

Argued Nov. 28, 2006.
Decided April 30, 2007.

Background: Exclusive licensee of patent for position-adjustable vehicle pedal assembly sued competitor for infringement. The United States District Court for the Eastern District of Michigan, 298 F.Supp.2d 581, granted summary judgment for competitor on the ground of obviousness. Licensee appealed. The United States Court of Appeals for the Federal Circuit, 119 Fed.Appx. 282, reversed. Certiorari was granted.

Holding: The Supreme Court, Justice Kennedy, held that patent was invalid as obvious.

Reversed and remanded.

West Headnotes

[1] Patents 291 ⇐26(1.1)

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k26 Combination
291k26(1.1) k. Use of Old or Well-Known Elements. Most Cited Cases
Patent claiming the combination of elements of prior art is obvious if the improvement is no more than the predictable use of prior art elements according to their established functions. 35 U.S.C.A. § 103.

[2] Patents 291 ⇐26(1.1)

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k26 Combination
291k26(1.1) k. Use of Old or Well-Known Elements. Most Cited Cases
Patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. 35 U.S.C.A. § 103.

[3] Patents 291 ⇐16.5(1)

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.5 State of Prior Art and Advancement Therein
291k16.5(1) k. In General. Most Cited Cases
In determining whether subject matter of patent claim is obvious, neither the particular motivation nor the avowed purpose of patentee controls; what matters is the objective reach of the claim. 35 U.S.C.A. § 103.

[4] Patents 291 ⇐16.5(4)

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.5 State of Prior Art and Advancement Therein
291k16.5(4) k. Remedying Defects or Solving Problems. Most Cited Cases
Patent's subject matter can be proved obvious by noting that there existed at time of invention a known problem for which there was an obvious solution encompassed by patent's claims. 35 U.S.C.A. § 103.

[5] Patents 291 ⇐16(3)

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16 Invention and Obviousness in General

291k16(3) k. View of Person Skilled in Art. Most Cited Cases

Patents 291 ⇐16.5(4)

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.5 State of Prior Art and Advancement Therein
291k16.5(4) k. Remedying Defects or Solving Problems. Most Cited Cases
In determining whether patent combining known elements is obvious, question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art; under correct analysis, any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide reason for combining the elements in the manner claimed. 35 U.S.C.A. § 103.

[6] Patents 291 ⇐16.5(4)

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.5 State of Prior Art and Advancement Therein
291k16.5(4) k. Remedying Defects or Solving Problems. Most Cited Cases

Patents 291 ⇐17(1)

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k17 Nature and Degree of Skill Involved
291k17(1) k. In General. Most Cited Cases
When there is design need or market pressure to solve a problem and there are finite number of identified, predictable solutions, person of ordinary skill has good reason to pursue the known options within his or her technical grasp, and if this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense; in that instance, the fact that a combination was obvious to try might show that patent for it was obvious. 35 U.S.C.A. § 103.

[7] Patents 291 ⇐16.22

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.22 k. Automobiles and Vehicles. Most Cited Cases
Patent claim disclosing position-adjustable pedal assembly with electronic pedal position sensor attached to support member of pedal assembly was invalid as obvious, in view of patent for adjustable pedal with a fixed pivot, and patent teaching a solution to wire chafing problems, namely locating the sensor on support structure; it was obvious to person of ordinary skill in the art to combine first patent with pivot-mounted pedal position sensor. 35 U.S.C.A. § 103.

[8] Patents 291 ⇐323.2(2)

291 Patents
291XII Infringement
291XII(C) Suits in Equity
291k323 Final Judgment or Decree
291k323.2 Summary Judgment
291k323.2(2) k. Presence or Absence of Fact Issues. Most Cited Cases
Where content of prior art, scope of patent claim, and level of ordinary skill in the art are not in material dispute, and obviousness of claim is apparent in light of these factors, summary judgment is appropriate. 35 U.S.C.A. § 103.

Patents 291 ⇐328(2)

291 Patents
291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents
291k328 Patents Enumerated
291k328(2) k. Original Utility. Most

Cited Cases
5,010,782, 5,063,811, 5,241,936, 5,385,068, 5,460,061, 5,819,593, 6,151,976. Cited as Prior Art.

Patents 291 ⚖328(2)

291 Patents
291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents
291k328 Patents Enumerated
291k328(2) k. Original Utility. Most Cited Cases
6,109,241. Cited.

Patents 291 ⚖328(2)

291 Patents
291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents
291k328 Patents Enumerated
291k328(2) k. Original Utility. Most Cited Cases
6,237,565. Invalid.

**1728 Syllabus* FN*

FN* The syllabus constitutes no part of the opinion of the Court but has been prepared by the Reporter of Decisions for the convenience of the reader. See *United States v. Detroit Timber & Lumber Co.*, 200 U.S. 321, 337, 26 S.Ct. 282, 50 L.Ed. 499.

To control a conventional automobile's speed, the driver depresses or releases the gas pedal, which interacts with the throttle via a cable or other mechanical link. Because the pedal's position in the footwell normally cannot be adjusted, a driver wishing to be closer or farther from it must either reposition himself in the seat ***1729** or move the seat, both of which can be imperfect solutions for smaller drivers in cars with deep footwells. This prompted inventors to design and patent pedals that could be adjusted to change their locations. The Asano patent reveals a support structure whereby, when the pedal location is adjusted, one of the pedal's pivot points stays fixed. Asano is also designed so that the force necessary to depress the pedal is the same regardless of location adjustments. The Redding patent reveals a different, sliding mechanism where both the pedal and the pivot point are adjusted.

In newer cars, computer-controlled throttles do not operate through force transferred from the pedal by a mechanical link, but open and close valves in response to electronic signals. For the computer to know what is happening with the pedal, an electronic sensor must translate the mechanical operation into digital data. Inventors had obtained a number of patents for such sensors. The so-called '936 patent taught that it was preferable to detect the pedal's position in the pedal mechanism, not in the engine, so the patent disclosed a pedal with an electronic sensor on a pivot point in the pedal assembly. The Smith patent taught that to prevent the wires connecting the sensor to the computer from chafing and wearing out, the sensor should be put on a fixed part of the pedal assembly rather than in or on the pedal's footpad. Inventors had also patented self-contained modular sensors, which can be taken off the shelf and attached to any mechanical pedal to allow it to function with a computer-controlled throttle. The '068 patent disclosed one such sensor. Chevrolet also manufactured trucks using modular sensors attached to the pedal support bracket, adjacent to the pedal and engaged with the pivot shaft about which the pedal rotates. Other patents disclose electronic sensors attached to adjustable pedal assemblies. For example, the Rixon patent locates the sensor in the pedal footpad, but is known for wire chafing.

After petitioner KSR developed an adjustable pedal system for cars with cable-actuated throttles and obtained its '976 patent for the design, General Motors Corporation (GMC) chose KSR to supply adjustable pedal systems for trucks using computer-controlled throttles. To make the '976 pedal compatible with the trucks, KSR added a modular sensor to its design. Respondents (Teleflex) hold the exclusive license for the Engelgau patent, claim 4 of which discloses a position-adjustable pedal as-

sembly with an electronic pedal position sensor attached a fixed pivot point. Despite having denied a similar, broader claim, the U.S. Patent and Trademark Office (PTO) had allowed claim 4 because it included the limitation of a fixed pivot position, which distinguished the design from Redding's. Asano was neither included among the Engelgau patent's prior art references nor mentioned in the patent's prosecution, and the PTO did not have before it an adjustable pedal with a fixed pivot point. After learning of KSR's design for GMC, Teleflex sued for infringement, asserting that KSR's pedal system infringed the Engelgau patent's claim 4. KSR countered that claim 4 was invalid under § 103 of the Patent Act, which forbids issuance of a patent when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art."

Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17-18, 86 S.Ct. 684, 15 L.Ed.2d 545, set out an objective analysis for applying § 103: "[T]he scope and content of the prior art are ... determined; differences between the prior art and the ***1730** claims at issue are ... ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." While the sequence of these questions might be reordered in any particular case, the factors define the controlling inquiry. However, seeking to resolve the obviousness question with more uniformity and consistency, the Federal Circuit has employed a "teaching, suggestion, or motivation" (TSM) test, under which a patent claim is only proved obvious if the prior art, the problem's nature, or the knowledge of a person having ordinary skill in the art reveals some motivation or suggestion to combine the prior art teachings.

The District Court granted KSR summary judgment. After reviewing pedal design history, the Engelgau patent's scope, and the relevant prior art, the court considered claim 4's validity, applying *Graham's* framework to determine whether under summary-judgment standards KSR had demonstrated that claim 4 was obvious. The court found "little difference" between the prior art's teachings and claim 4: Asano taught everything contained in the claim except using a sensor to detect the pedal's position and transmit it to a computer controlling the throttle. That additional aspect was revealed in, *e.g.,* the '068 patent and Chevrolet's sensors. The court then held that KSR satisfied the TSM test, reasoning (1) the state of the industry would lead inevitably to combinations of electronic sensors and adjustable pedals, (2) Rixon provided the basis for these developments, and (3) Smith taught a solution to Rixon's chafing problems by positioning the sensor on the pedal's fixed structure, which could lead to the combination of a pedal like Asano with a pedal position sensor.

Reversing, the Federal Circuit ruled the District Court had not applied the TSM test strictly enough, having failed to make findings as to the specific understanding or principle within a skilled artisan's knowledge that would have motivated one with no knowledge of the invention to attach an electronic control to the Asano assembly's support bracket. The Court of Appeals held that the District Court's recourse to the nature of the problem to be solved was insufficient because, unless the prior art references addressed the precise problem that the patentee was trying to solve, the problem would not motivate an inventor to look at those references. The appeals court found that the Asano pedal was designed to ensure that the force required to depress the pedal is the same no matter how the pedal is adjusted, whereas Engelgau sought to provide a simpler, smaller, cheaper adjustable electronic pedal. The Rixon pedal, said the court, suffered from chafing but was not designed to solve that problem and taught nothing helpful to Engelgau's purpose. Smith, in turn, did not relate to adjustable pedals

and did not necessarily go to the issue of motivation to attach the electronic control on the pedal assembly's support bracket. So interpreted, the court held, the patents would not have led a person of ordinary skill to put a sensor on an Asano-like pedal. That it might have been obvious to try that combination was likewise irrelevant. Finally, the court held that genuine issues of material fact precluded summary judgment.

Held: The Federal Circuit addressed the obviousness question in a narrow, rigid manner that is inconsistent with § 103 and this Court's precedents. KSR provided ***1731** convincing evidence that mounting an available sensor on a fixed pivot point of the Asano pedal was a design step well within the grasp of a person of ordinary skill in the relevant art and that the benefit of doing so would be obvious. Its arguments, and the record, demonstrate that the Engelgau patent's claim 4 is obvious. Pp. 1739 - 1746.

1. *Graham* provided an expansive and flexible approach to the obviousness question that is inconsistent with the way the Federal Circuit applied its TSM test here. Neither § 103's enactment nor *Graham's* analysis disturbed the Court's earlier instructions concerning the need for caution in granting a patent based on the combination of elements found in the prior art. See *Great Atlantic & Pacific Tea Co. v. Supermarket Equipment Corp.*, 340 U.S. 147, 152, 71 S.Ct. 127, 95 L.Ed. 162. Such a combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. See, *e.g.*, *United States v. Adams*, 383 U.S. 39, 50-52, 86 S.Ct. 708, 15 L.Ed.2d 572. When a work is available in one field, design incentives and other market forces can prompt variations of it, either in the same field or in another. If a person of ordinary skill in the art can implement a predictable variation, and would see the benefit of doing so, § 103 likely bars its patentability. Moreover, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill. A court must ask whether the improvement is more than the predictable use of prior-art elements according to their established functions. Following these principles may be difficult if the claimed subject matter involves more than the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for the improvement. To determine whether there was an apparent reason to combine the known elements in the way a patent claims, it will often be necessary to look to interrelated teachings of multiple patents; to the effects of demands known to the design community or present in the marketplace; and to the background knowledge possessed by a person having ordinary skill in the art. To facilitate review, this analysis should be made explicit. But it need not seek out precise teachings directed to the challenged claim's specific subject matter, for a court can consider the inferences and creative steps a person of ordinary skill in the art would employ. Pp. 1739 - 1741.

(b) The TSM test captures a helpful insight: A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art. Although common sense directs caution as to a patent application claiming as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does. Inventions usually rely upon building blocks long since uncovered, and claimed discoveries almost necessarily will be combinations of what, in some sense, is already known. Helpful insights, however, need not become rigid and mandatory formulas. If it is so applied, the TSM test is incompatible with this Court's precedents. The diversity of inventive pursuits and of modern technology counsels against confining the obviousness analysis by a formalistic conception of the words

teaching, suggestion, and motivation, or by overemphasizing the importance of published articles and the explicit ***1732** content of issued patents. In many fields there may be little discussion of obvious techniques or combinations, and market demand, rather than scientific literature, may often drive design trends. Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, for patents combining previously known elements, deprive prior inventions of their value or utility. Since the TSM test was devised, the Federal Circuit doubtless has applied it in accord with these principles in many cases. There is no necessary inconsistency between the test and the *Graham* analysis. But a court errs where, as here, it transforms general principle into a rigid rule limiting the obviousness inquiry. Pp. 1740 - 1741.

(c) The flaws in the Federal Circuit's analysis relate mostly to its narrow conception of the obviousness inquiry consequent in its application of the TSM test. The Circuit first erred in holding that courts and patent examiners should look only to the problem the patentee was trying to solve. Under the correct analysis, any need or problem known in the field and addressed by the patent can provide a reason for combining the elements in the manner claimed. Second, the appeals court erred in assuming that a person of ordinary skill in the art attempting to solve a problem will be led only to those prior art elements designed to solve the same problem. The court wrongly concluded that because Asano's primary purpose was solving the constant ratio problem, an inventor considering how to put a sensor on an adjustable pedal would have no reason to consider putting it on the Asano pedal. It is common sense that familiar items may have obvious uses beyond their primary purposes, and a person of ordinary skill often will be able to fit the teachings of multiple patents together like pieces of a puzzle. Regardless of Asano's primary purpose, it provided an obvious example of an adjustable pedal with a fixed pivot point, and the prior art was replete with patents indicating that such a point was an ideal mount for a sensor. Third, the court erred in concluding that a patent claim cannot be proved obvious merely by showing that the combination of elements was obvious to try. When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. Finally, the court drew the wrong conclusion from the risk of courts and patent examiners falling prey to hindsight bias. Rigid preventative rules that deny recourse to common sense are neither necessary under, nor consistent with, this Court's case law. Pp. 1741 - 1743.

2. Application of the foregoing standards demonstrates that claim 4 is obvious. Pp. 1743 - 1746.

(a) The Court rejects Teleflex's argument that the Asano pivot mechanism's design prevents its combination with a sensor in the manner claim 4 describes. This argument was not raised before the District Court, and it is unclear whether it was raised before the Federal Circuit. Given the significance of the District Court's finding that combining Asano with a pivot-mounted pedal position sensor fell within claim 4's scope, it is apparent that Teleflex would have made clearer challenges if it intended to preserve this claim. Its failure to clearly raise the argument, and the appeals court's silence on the issue, lead this Court to accept the District Court's conclusion. Pp. 1743 - 1744.

***1733** (b) The District Court correctly concluded that when Engelgau designed the claim 4 subject matter, it was obvious to a person of ordinary skill in the art to combine Asano with a pivot-mounted pedal position sensor. There then was a marketplace creating a strong incentive to convert mechanical pedals to electronic pedals, and the prior art taught a number of methods for doing so. The Federal Circuit considered the issue too narrowly by, in effect, asking whether a pedal designer writing on a

blank slate would have chosen both Asano and a modular sensor similar to the ones used in the Chevrolet trucks and disclosed in the '068 patent. The proper question was whether a pedal designer of ordinary skill in the art, facing the wide range of needs created by developments in the field, would have seen an obvious benefit to upgrading Asano with a sensor. For such a designer starting with Asano, the question was where to attach the sensor. The '936 patent taught the utility of putting the sensor on the pedal device. Smith, in turn, explained not to put the sensor on the pedal footpad, but instead on the structure. And from Rixon's known wire-chafing problems, and Smith's teaching that the pedal assemblies must not precipitate any motion in the connecting wires, the designer would know to place the sensor on a nonmoving part of the pedal structure. The most obvious such point is a pivot point. The designer, accordingly, would follow Smith in mounting the sensor there. Just as it was possible to begin with the objective to upgrade Asano to work with a computer-controlled throttle, so too was it possible to take an adjustable electronic pedal like Rixon and seek an improvement that would avoid the wire-chafing problem. Teleflex has not shown anything in the prior art that taught away from the use of Asano, nor any secondary factors to dislodge the determination that claim 4 is obvious. Pp. 1744 - 1746.

3. The Court disagrees with the Federal Circuit's holding that genuine issues of material fact precluded summary judgment. The ultimate judgment of obviousness is a legal determination. *Graham*, 383 U.S., at 17, 86 S.Ct. 684. Where, as here, the prior art's content, the patent claim's scope, and the level of ordinary skill in the art are not in material dispute and the claim's obviousness is apparent, summary judgment is appropriate. Pp. 1745 - 1746.

119 Fed.Appx. 282, reversed and remanded.

KENNEDY, J., delivered the opinion for a unanimous Court.

James W. Dabney, for petitioner.

Thomas G. Hungar, for the United States as amicus curiae, by special leave of the Court, supporting the petitioner.

Thomas C. Goldstein, for respondents.

John F. Duffy, Fried, Frank, Harris, Shriver & Jacobson LLP, Of Counsel, James W. Dabney, Counsel of Record, New York, New York, Stephen S. Rabinowitz, Henry C. Lebowitz, Mitchell E. Epner, Darcy M. Goddard, Fried, Frank, Harris, Shriver & Jacobson LLP, New York, New York, Attorneys for Petitioner.

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For U.S. Supreme Court briefs, see:2006 WL 2515631 (Pet.Brief)2006 WL 2989549 (Resp.Brief)2006 WL 3367870 (Reply.Brief)2006 WL 3146709 (Resp.Supp.Brief)

Justice KENNEDY delivered the opinion of the Court.

Teleflex Incorporated and its subsidiary Technology Holding Company-both referred to here as Teleflex-sued KSR International Company for patent infringement. The patent at issue, United States Patent No. 6,237,565 B1, is entitled "Adjustable Pedal Assembly With Electronic Throttle Control." Supplemental App. 1. The patentee is Steven J. Engelgau, and the patent is referred to as "the Engelgau patent." Teleflex holds the exclusive license to the patent.

Claim 4 of the Engelgau patent describes a mechanism for combining an electronic sensor with an adjustable automobile pedal so the pedal's position can be transmitted to a computer that controls the throttle in the vehicle's engine. When Teleflex accused KSR of infringing the Engelgau patent by adding an electronic sensor to one of KSR's previously designed pedals, KSR countered that claim 4 was invalid under the Patent Act, 35 U.S.C. § 103, because its subject matter was obvious.

Section 103 forbids issuance of a patent when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains."

In *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966), the Court set out a framework for applying the statutory language of § 103, language itself based on the logic of the earlier decision in *Hotchkiss v. Greenwood*, 11 How. 248, 13 L.Ed. 683 (1851), and its progeny. See 383 U.S., at 15-17, 86 S.Ct. 684. The analysis is objective:

"Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Id.*, at 17-18, 86 S.Ct. 684.

While the sequence of these questions might be reordered in any particular case, the factors continue to define the inquiry that controls. If a court, or patent examiner, conducts this analysis and concludes the claimed subject matter was obvious, the claim is invalid under § 103.

Seeking to resolve the question of obviousness with more uniformity and consistency, the Court of Appeals for the Federal Circuit has employed an approach referred to by the parties as the "teaching, suggestion, or motivation" test (TSM test), under which a patent claim is only proved obvious if "some motivation or suggestion to combine the prior art teachings" can be found in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art. See, *e.g.*, *Al-Site Corp. v. VSI Int'l, Inc.*, 174 F.3d 1308, 1323-1324 (C.A.Fed.1999). KSR challenges that ***1735** test, or at least its application in this case. See 119 Fed.Appx. 282, 286-290 (C.A.Fed.2005). Because the Court of Appeals addressed the question of obviousness in a manner contrary to § 103 and our precedents, we granted certiorari, 547 U.S. ----, 126 S.Ct. 2965, 165 L.Ed.2d 949 (2006). We now reverse.

I

A

In car engines without computer-controlled throttles, the accelerator pedal interacts with the throttle via cable or other mechanical link. The pedal arm acts as a lever rotating around a pivot point. In a cable-actuated throttle control the rotation caused by pushing down the pedal pulls a cable, which in turn pulls open valves in the carburetor or fuel injection unit. The wider the valves open, the more fuel and air are released, causing combustion to increase and the car to accelerate. When the driver takes his foot off the pedal, the opposite occurs as the cable is released and the valves slide closed.

In the 1990's it became more common to install computers in cars to control engine operation. Computer-controlled throttles open and close valves in response to electronic signals, not through

force transferred from the pedal by a mechanical link. Constant, delicate adjustments of air and fuel mixture are possible. The computer's rapid processing of factors beyond the pedal's position improves fuel efficiency and engine performance.

For a computer-controlled throttle to respond to a driver's operation of the car, the computer must know what is happening with the pedal. A cable or mechanical link does not suffice for this purpose; at some point, an electronic sensor is necessary to translate the mechanical operation into digital data the computer can understand.

Before discussing sensors further we turn to the mechanical design of the pedal itself. In the traditional design a pedal can be pushed down or released but cannot have its position in the footwell adjusted by sliding the pedal forward or back. As a result, a driver who wishes to be closer or farther from the pedal must either reposition himself in the driver's seat or move the seat in some way. In cars with deep footwells these are imperfect solutions for drivers of smaller stature. To solve the problem, inventors, beginning in the 1970's, designed pedals that could be adjusted to change their location in the footwell. Important for this case are two adjustable pedals disclosed in U.S. Patent Nos. 5,010,782 (filed July 28, 1989) (Asano) and 5,460,061 (filed Sept. 17, 1993) (Redding). The Asano patent reveals a support structure that houses the pedal so that even when the pedal location is adjusted relative to the driver, one of the pedal's pivot points stays fixed. The pedal is also designed so that the force necessary to push the pedal down is the same regardless of adjustments to its location. The Redding patent reveals a different, sliding mechanism where both the pedal and the pivot point are adjusted.

We return to sensors. Well before Engelgau applied for his challenged patent, some inventors had obtained patents involving electronic pedal sensors for computer-controlled throttles. These inventions, such as the device disclosed in U.S. Patent No. 5,241,936 (filed Sept. 9, 1991) ('936), taught that it was preferable to detect the pedal's position in the pedal assembly, not in the engine. The '936 patent disclosed a pedal with an electronic sensor on a pivot point in the pedal assembly. U.S. Patent No. 5,063,811 (filed July 9, 1990) (Smith) taught that to prevent the ***1736** wires connecting the sensor to the computer from chafing and wearing out, and to avoid grime and damage from the driver's foot, the sensor should be put on a fixed part of the pedal assembly rather than in or on the pedal's footpad.

In addition to patents for pedals with integrated sensors inventors obtained patents for self-contained modular sensors. A modular sensor is designed independently of a given pedal so that it can be taken off the shelf and attached to mechanical pedals of various sorts, enabling the pedals to be used in automobiles with computer-controlled throttles. One such sensor was disclosed in U.S. Patent No. 5,385,068 (filed Dec. 18, 1992) ('068). In 1994, Chevrolet manufactured a line of trucks using modular sensors "attached to the pedal support bracket, adjacent to the pedal and engaged with the pivot shaft about which the pedal rotates in operation." 298 F.Supp.2d 581, 589 (E.D.Mich.2003).

The prior art contained patents involving the placement of sensors on adjustable pedals as well. For example, U.S. Patent No. 5,819,593 (filed Aug. 17, 1995) (Rixon) discloses an adjustable pedal assembly with an electronic sensor for detecting the pedal's position. In the Rixon pedal the sensor is located in the pedal footpad. The Rixon pedal was known to suffer from wire chafing when the pedal was depressed and released.

This short account of pedal and sensor technology leads to the instant case.

B

KSR, a Canadian company, manufactures and supplies auto parts, including pedal systems. Ford Motor Company hired KSR in 1998 to supply an adjustable pedal system for various lines of automo-

biles with cable-actuated throttle controls. KSR developed an adjustable mechanical pedal for Ford and obtained U.S. Patent No. 6,151,976 (filed July 16, 1999) ('976) for the design. In 2000, KSR was chosen by General Motors Corporation (GMC or GM) to supply adjustable pedal systems for Chevrolet and GMC light trucks that used engines with computer-controlled throttles. To make the '976 pedal compatible with the trucks, KSR merely took that design and added a modular sensor.

Teleflex is a rival to KSR in the design and manufacture of adjustable pedals. As noted, it is the exclusive licensee of the Engelgau patent. Engelgau filed the patent application on August 22, 2000 as a continuation of a previous application for U.S. Patent No. 6,109,241, which was filed on January 26, 1999. He has sworn he invented the patent's subject matter on February 14, 1998. The Engelgau patent discloses an adjustable electronic pedal described in the specification as a "simplified vehicle control pedal assembly that is less expensive, and which uses fewer parts and is easier to package within the vehicle." Engelgau, col. 2, lines 2-5, Supplemental App. 6. Claim 4 of the patent, at issue here, describes:

"A vehicle control pedal apparatus comprising:

a support adapted to be mounted to a vehicle structure;

an adjustable pedal assembly having a pedal arm moveable in for[e] and aft directions with respect to said support;

a pivot for pivotally supporting said adjustable pedal assembly with respect to said support and defining a pivot axis; and

an electronic control attached to said support for controlling a vehicle system;

said apparatus characterized by said electronic control being responsive to said pivot for providing a signal that corresponds to pedal arm position as said pedal arm pivots about said pivot ***1737** axis between rest and applied positions wherein the position of said pivot remains constant while said pedal arm moves in fore and aft directions with respect to said pivot." *Id.*, col. 6, lines 17-36, Supplemental App. 8 (diagram numbers omitted).

We agree with the District Court that the claim discloses "a position-adjustable pedal assembly with an electronic pedal position sensor attached to the support member of the pedal assembly. Attaching the sensor to the support member allows the sensor to remain in a fixed position while the driver adjusts the pedal." 298 F.Supp.2d, at 586-587.

Before issuing the Engelgau patent the U.S. Patent and Trademark Office (PTO) rejected one of the patent claims that was similar to, but broader than, the present claim 4. The claim did not include the requirement that the sensor be placed on a fixed pivot point. The PTO concluded the claim was an obvious combination of the prior art disclosed in Redding and Smith, explaining:

" 'Since the prior ar[t] references are from the field of endeavor, the purpose disclosed ... would have been recognized in the pertinent art of Redding. Therefore it would have been obvious ... to provide the device of Redding with the ... means attached to a support member as taught by Smith.' " *Id.*, at 595.

In other words Redding provided an example of an adjustable pedal and Smith explained how to mount a sensor on a pedal's support structure, and the rejected patent claim merely put these two teachings together.

Although the broader claim was rejected, claim 4 was later allowed because it included the limitation of a fixed pivot point, which distinguished the design from Redding's. *Ibid.* Engelgau had not included Asano among the prior art references, and Asano was not mentioned in the patent's prosecution. Thus, the PTO did not have before it an adjustable pedal with a fixed pivot point. The patent issued on May 29, 2001 and was assigned to Tele-

flex.

Upon learning of KSR's design for GM, Teleflex sent a warning letter informing KSR that its proposal would violate the Engelgau patent. " 'Teleflex believes that any supplier of a product that combines an adjustable pedal with an electronic throttle control necessarily employs technology covered by one or more' " of Teleflex's patents. *Id.*, at 585. KSR refused to enter a royalty arrangement with Teleflex; so Teleflex sued for infringement, asserting KSR's pedal infringed the Engelgau patent and two other patents. *Ibid.* Teleflex later abandoned its claims regarding the other patents and dedicated the patents to the public. The remaining contention was that KSR's pedal system for GM infringed claim 4 of the Engelgau patent. Teleflex has not argued that the other three claims of the patent are infringed by KSR's pedal, nor has Teleflex argued that the mechanical adjustable pedal designed by KSR for Ford infringed any of its patents.

C

The District Court granted summary judgment in KSR's favor. After reviewing the pertinent history of pedal design, the scope of the Engelgau patent, and the relevant prior art, the court considered the validity of the contested claim. By direction of 35 U.S.C. § 282, an issued patent is presumed valid. The District Court applied *Graham's* framework to determine whether under summary-judgment standards KSR had overcome the presumption and demonstrated that claim 4 was obvious in light of the prior art in existence when ***1738** the claimed subject matter was invented. See § 102(a).

The District Court determined, in light of the expert testimony and the parties' stipulations, that the level of ordinary skill in pedal design was " 'an undergraduate degree in mechanical engineering (or an equivalent amount of industry experience) [and] familiarity with pedal control systems for vehicles.' " 298 F.Supp.2d, at 590. The court then set forth the relevant prior art, including the patents and pedal designs described above.

Following *Graham's* direction, the court compared the teachings of the prior art to the claims of Engelgau. It found "little difference." 298 F.Supp.2d, at 590. Asano taught everything contained in claim 4 except the use of a sensor to detect the pedal's position and transmit it to the computer controlling the throttle. That additional aspect was revealed in sources such as the '068 patent and the sensors used by Chevrolet.

Under the controlling cases from the Court of Appeals for the Federal Circuit, however, the District Court was not permitted to stop there. The court was required also to apply the TSM test. The District Court held KSR had satisfied the test. It reasoned (1) the state of the industry would lead inevitably to combinations of electronic sensors and adjustable pedals, (2) Rixon provided the basis for these developments, and (3) Smith taught a solution to the wire chafing problems in Rixon, namely locating the sensor on the fixed structure of the pedal. This could lead to the combination of Asano, or a pedal like it, with a pedal position sensor.

The conclusion that the Engelgau design was obvious was supported, in the District Court's view, by the PTO's rejection of the broader version of claim 4. Had Engelgau included Asano in his patent application, it reasoned, the PTO would have found claim 4 to be an obvious combination of Asano and Smith, as it had found the broader version an obvious combination of Redding and Smith. As a final matter, the District Court held that the secondary factor of Teleflex's commercial success with pedals based on Engelgau's design did not alter its conclusion. The District Court granted summary judgment for KSR.

With principal reliance on the TSM test, the Court of Appeals reversed. It ruled the District Court had not been strict enough in applying the test, having failed to make " 'finding[s] as to the specific understanding or principle within the knowledge of a skilled artisan that would have motivated one with

no knowledge of [the] invention'... to attach an electronic control to the support bracket of the Asano assembly." 119 Fed.Appx., at 288 (brackets in original) (quoting *In re Kotzab*, 217 F.3d 1365, 1371 (C.A.Fed.2000)). The Court of Appeals held that the District Court was incorrect that the nature of the problem to be solved satisfied this requirement because unless the "prior art references address[ed] the precise problem that the patentee was trying to solve," the problem would not motivate an inventor to look at those references. 119 Fed.Appx., at 288.

Here, the Court of Appeals found, the Asano pedal was designed to solve the " 'constant ratio problem' "-that is, to ensure that the force required to depress the pedal is the same no matter how the pedal is adjusted-whereas Engelgau sought to provide a simpler, smaller, cheaper adjustable electronic pedal. *Ibid.* As for Rixon, the court explained, that pedal suffered from the problem of wire chafing but was not designed to solve it. In the court's view Rixon did not teach anything helpful to Engelgau's purpose. Smith, in turn, did not relate to adjustable pedals and did not "necessarily go to the issue of motivation ***1739** to attach the electronic control on the support bracket of the pedal assembly." *Ibid.* When the patents were interpreted in this way, the Court of Appeals held, they would not have led a person of ordinary skill to put a sensor on the sort of pedal described in Asano.

That it might have been obvious to try the combination of Asano and a sensor was likewise irrelevant, in the court's view, because " ' "[o]bvious to try" has long been held not to constitute obviousness.' " *Id.*, at 289 (quoting *In re Deuel*, 51 F.3d 1552, 1559 (C.A.Fed.1995)).

The Court of Appeals also faulted the District Court's consideration of the PTO's rejection of the broader version of claim 4. The District Court's role, the Court of Appeals explained, was not to speculate regarding what the PTO might have done had the Engelgau patent mentioned Asano. Rather, the court held, the District Court was obliged first to presume that the issued patent was valid and then to render its own independent judgment of obviousness based on a review of the prior art. The fact that the PTO had rejected the broader version of claim 4, the Court of Appeals said, had no place in that analysis.

The Court of Appeals further held that genuine issues of material fact precluded summary judgment. Teleflex had proffered statements from one expert that claim 4 " 'was a simple, elegant, and novel combination of features,' "119 Fed.Appx., at 290, compared to Rixon, and from another expert that claim 4 was nonobvious because, unlike in Rixon, the sensor was mounted on the support bracket rather than the pedal itself. This evidence, the court concluded, sufficed to require a trial.

II

A

We begin by rejecting the rigid approach of the Court of Appeals. Throughout this Court's engagement with the question of obviousness, our cases have set forth an expansive and flexible approach inconsistent with the way the Court of Appeals applied its TSM test here. To be sure, *Graham* recognized the need for "uniformity and definiteness." 383 U.S., at 18, 86 S.Ct. 684. Yet the principles laid down in *Graham* reaffirmed the "functional approach" of *Hotchkiss*, 11 How. 248, 13 L.Ed. 683. See 383 U.S., at 12, 86 S.Ct. 684. To this end, *Graham* set forth a broad inquiry and invited courts, where appropriate, to look at any secondary considerations that would prove instructive. *Id.*, at 17, 86 S.Ct. 684.

Neither the enactment of § 103 nor the analysis in *Graham* disturbed this Court's earlier instructions concerning the need for caution in granting a patent based on the combination of elements found in the prior art. For over a half century, the Court has held that a "patent for a combination which only unites

old elements with no change in their respective functions ... obviously withdraws what is already known into the field of its monopoly and diminishes the resources available to skillful men." *Great Atlantic & Pacific Tea Co. v. Supermarket Equipment Corp.*, 340 U.S. 147, 152, 71 S.Ct. 127, 95 L.Ed. 162 (1950). This is a principal reason for declining to allow patents for what is obvious. The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. Three cases decided after *Graham* illustrate the application of this doctrine.

In *United States v. Adams*, 383 U.S. 39, 40, 86 S.Ct. 708, 15 L.Ed.2d 572 (1966), a companion case to *Graham*, the Court considered the obviousness of a "wet battery" that varied from prior designs in two ways: ***1740** It contained water, rather than the acids conventionally employed in storage batteries; and its electrodes were magnesium and cuprous chloride, rather than zinc and silver chloride. The Court recognized that when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result. 383 U.S., at 50-51, 86 S.Ct. 708. It nevertheless rejected the Government's claim that Adams's battery was obvious. The Court relied upon the corollary principle that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious. *Id.*, at 51-52, 86 S.Ct. 708. When Adams designed his battery, the prior art warned that risks were involved in using the types of electrodes he employed. The fact that the elements worked together in an unexpected and fruitful manner supported the conclusion that Adams's design was not obvious to those skilled in the art.

In *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 90 S.Ct. 305, 24 L.Ed.2d 258 (1969), the Court elaborated on this approach. The subject matter of the patent before the Court was a device combining two pre-existing elements: a radiant-heat burner and a paving machine. The device, the Court concluded, did not create some new synergy: The radiant-heat burner functioned just as a burner was expected to function; and the paving machine did the same. The two in combination did no more than they would in separate, sequential operation. *Id.*, at 60-62, 90 S.Ct. 305. In those circumstances, "while the combination of old elements performed a useful function, it added nothing to the nature and quality of the radiant-heat burner already patented," and the patent failed under § 103. *Id.*, at 62, 90 S.Ct. 305 (footnote omitted).

Finally, in *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 96 S.Ct. 1532, 47 L.Ed.2d 784 (1976), the Court derived from the precedents the conclusion that when a patent "simply arranges old elements with each performing the same function it had been known to perform" and yields no more than one would expect from such an arrangement, the combination is obvious. *Id.*, at 282, 96 S.Ct. 1532.

[1] The principles underlying these cases are instructive when the question is whether a patent claiming the combination of elements of prior art is obvious. When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *Sakraida* and *Anderson's-Black Rock* are illustrative-a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.

Following these principles may be more difficult in other cases than it is here because the claimed subject matter may involve more than the simple sub-

stitution of one known element for another or the mere application of a known technique to a piece of prior art ready for the improvement. Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ***1741** ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. See *In re Kahn,* 441 F.3d 977, 988 (C.A.Fed.2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"). As our precedents make clear, however, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.

B

[2] When it first established the requirement of demonstrating a teaching, suggestion, or motivation to combine known elements in order to show that the combination is obvious, the Court of Customs and Patent Appeals captured a helpful insight. See *Application of Bergel,* 48 C.C.P.A. 1102, 292 F.2d 955, 956-957 (1961). As is clear from cases such as *Adams,* a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

Helpful insights, however, need not become rigid and mandatory formulas; and when it is so applied, the TSM test is incompatible with our precedents. The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents. The diversity of inventive pursuits and of modern technology counsels against limiting the analysis in this way. In many fields it may be that there is little discussion of obvious techniques or combinations, and it often may be the case that market demand, rather than scientific literature, will drive design trends. Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility.

In the years since the Court of Customs and Patent Appeals set forth the essence of the TSM test, the Court of Appeals no doubt has applied the test in accord with these principles in many cases. There is no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis. But when a court transforms the general principle into a rigid rule that limits the obviousness inquiry, as the Court of Appeals did here, it errs.

C

[3][4] The flaws in the analysis of the Court of Appeals relate for the most part to the court's narrow conception of the obviousness inquiry reflected in its application of the TSM test. In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the ***1742** patentee controls. What matters is the objective reach of the claim. If

the claim extends to what is obvious, it is invalid under § 103. One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims.

[5] The first error of the Court of Appeals in this case was to foreclose this reasoning by holding that courts and patent examiners should look only to the problem the patentee was trying to solve. 119 Fed.Appx., at 288. The Court of Appeals failed to recognize that the problem motivating the patentee may be only one of many addressed by the patent's subject matter. The question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art. Under the correct analysis, any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.

The second error of the Court of Appeals lay in its assumption that a person of ordinary skill attempting to solve a problem will be led only to those elements of prior art designed to solve the same problem. *Ibid.* The primary purpose of Asano was solving the constant ratio problem; so, the court concluded, an inventor considering how to put a sensor on an adjustable pedal would have no reason to consider putting it on the Asano pedal. *Ibid.* Common sense teaches, however, that familiar items may have obvious uses beyond their primary purposes, and in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle. Regardless of Asano's primary purpose, the design provided an obvious example of an adjustable pedal with a fixed pivot point; and the prior art was replete with patents indicating that a fixed pivot point was an ideal mount for a sensor. The idea that a designer hoping to make an adjustable electronic pedal would ignore Asano because Asano was designed to solve the constant ratio problem makes little sense. A person of ordinary skill is also a person of ordinary creativity, not an automaton.

[6] The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." *Id.*, at 289 (internal quotation marks omitted). When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

The Court of Appeals, finally, drew the wrong conclusion from the risk of courts and patent examiners falling prey to hindsight bias. A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. See *Graham*, 383 U.S., at 36, 86 S.Ct. 684 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to " 'guard against slipping into the use of hindsight' " (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412 (C.A.6 1964))). Rigid preventative rules that deny factfinders recourse to common sense, however, are ***1743** neither necessary under our case law nor consistent with it.

We note the Court of Appeals has since elaborated a broader conception of the TSM test than was applied in the instant matter. See, *e.g.*, *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1367 (2006) ("Our suggestion test is in actuality quite flexible and not only permits, but *requires*, consideration of common knowledge and common sense"); *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1291 (2006) ("There is flexibility in our obviousness jurispru-

dence because a motivation may be found *implicitly* in the prior art. We do not have a rigid test that requires an actual teaching to combine ..."). Those decisions, of course, are not now before us and do not correct the errors of law made by the Court of Appeals in this case. The extent to which they may describe an analysis more consistent with our earlier precedents and our decision here is a matter for the Court of Appeals to consider in its future cases. What we hold is that the fundamental misunderstandings identified above led the Court of Appeals in this case to apply a test inconsistent with our patent law decisions.

III

[7] When we apply the standards we have explained to the instant facts, claim 4 must be found obvious. We agree with and adopt the District Court's recitation of the relevant prior art and its determination of the level of ordinary skill in the field. As did the District Court, we see little difference between the teachings of Asano and Smith and the adjustable electronic pedal disclosed in claim 4 of the Engelgau patent. A person having ordinary skill in the art could have combined Asano with a pedal position sensor in a fashion encompassed by claim 4, and would have seen the benefits of doing so.

A

Teleflex argues in passing that the Asano pedal cannot be combined with a sensor in the manner described by claim 4 because of the design of Asano's pivot mechanisms. See Brief for Respondents 48-49, and n. 17. Therefore, Teleflex reasons, even if adding a sensor to Asano was obvious, that does not establish that claim 4 encompasses obvious subject matter. This argument was not, however, raised before the District Court. There Teleflex was content to assert only that the problem motivating the invention claimed by the Engelgau patent would not lead to the solution of combining of Asano with a sensor. See Teleflex's Response to KSR's Motion for Summary Judgment of Invalidity in No. 02-74586 (ED Mich.), pp. 18-20, App. 144a-146a. It is also unclear whether the current argument was raised before the Court of Appeals, where Teleflex advanced the nonspecific, conclusory contention that combining Asano with a sensor would not satisfy the limitations of claim 4. See Brief for Plaintiffs-Appellants in No. 04-1152 (CA Fed.), pp. 42-44. Teleflex's own expert declarations, moreover, do not support the point Teleflex now raises. See Declaration of Clark J. Radcliffe, Ph.D., Supplemental App. 204-207; Declaration of Timothy L. Andresen, *id.*, at 208-210. The only statement in either declaration that might bear on the argument is found in the Radcliffe declaration:

> "Asano ... and Rixon ... are complex mechanical linkage-based devices that are expensive to produce and assemble and difficult to package. It is exactly these difficulties with prior art designs that [Engelgau] resolves. The use of an adjustable pedal with a single pivot reflecting pedal position combined with an electronic control mounted between the ***1744** support and the adjustment assembly at that pivot was a simple, elegant, and novel combination of features in the Engelgau '565 patent." *Id.*, at 206, ¶ 16.

Read in the context of the declaration as a whole this is best interpreted to mean that Asano could not be used to solve "[t]he problem addressed by Engelgau '565[:] to provide a less expensive, more quickly assembled, and smaller package adjustable pedal assembly with electronic control." *Id.*, at 205, ¶ 10.

The District Court found that combining Asano with a pivot-mounted pedal position sensor fell within the scope of claim 4. 298 F.Supp.2d, at 592-593. Given the sigificance of that finding to the District Court's judgment, it is apparent that Teleflex would have made clearer challenges to it if it intended to preserve this claim. In light of Teleflex's failure to raise the argument in a clear fashion, and the silence of the Court of Appeals on the issue, we take the District Court's conclusion on the

point to be correct.

B

The District Court was correct to conclude that, as of the time Engelgau designed the subject matter in claim 4, it was obvious to a person of ordinary skill to combine Asano with a pivot-mounted pedal position sensor. There then existed a marketplace that created a strong incentive to convert mechanical pedals to electronic pedals, and the prior art taught a number of methods for achieving this advance. The Court of Appeals considered the issue too narrowly by, in effect, asking whether a pedal designer writing on a blank slate would have chosen both Asano and a modular sensor similar to the ones used in the Chevrolet truckline and disclosed in the '068 patent. The District Court employed this narrow inquiry as well, though it reached the correct result nevertheless. The proper question to have asked was whether a pedal designer of ordinary skill, facing the wide range of needs created by developments in the field of endeavor, would have seen a benefit to upgrading Asano with a sensor.

In automotive design, as in many other fields, the interaction of multiple components means that changing one component often requires the others to be modified as well. Technological developments made it clear that engines using computer-controlled throttles would become standard. As a result, designers might have decided to design new pedals from scratch; but they also would have had reason to make pre-existing pedals work with the new engines. Indeed, upgrading its own pre-existing model led KSR to design the pedal now accused of infringing the Engelgau patent.

For a designer starting with Asano, the question was where to attach the sensor. The consequent legal question, then, is whether a pedal designer of ordinary skill starting with Asano would have found it obvious to put the sensor on a fixed pivot point. The prior art discussed above leads us to the conclusion that attaching the sensor where both KSR and Engelgau put it would have been obvious to a person of ordinary skill.

The '936 patent taught the utility of putting the sensor on the pedal device, not in the engine. Smith, in turn, explained to put the sensor not on the pedal's footpad but instead on its support structure. And from the known wire-chafing problems of Rixon, and Smith's teaching that "the pedal assemblies must not precipitate any motion in the connecting wires," Smith, col. 1, lines 35-37, Supplemental App. 274, the designer would know to place the sensor on a nonmoving part of the pedal structure. The most obvious nonmoving point on the structure from which a sensor can ***1745** easily detect the pedal's position is a pivot point. The designer, accordingly, would follow Smith in mounting the sensor on a pivot, thereby designing an adjustable electronic pedal covered by claim 4.

Just as it was possible to begin with the objective to upgrade Asano to work with a computer-controlled throttle, so too was it possible to take an adjustable electronic pedal like Rixon and seek an improvement that would avoid the wire-chafing problem. Following similar steps to those just explained, a designer would learn from Smith to avoid sensor movement and would come, thereby, to Asano because Asano disclosed an adjustable pedal with a fixed pivot.

Teleflex indirectly argues that the prior art taught away from attaching a sensor to Asano because Asano in its view is bulky, complex, and expensive. The only evidence Teleflex marshals in support of this argument, however, is the Radcliffe declaration, which merely indicates that Asano would not have solved Engelgau's goal of making a small, simple, and inexpensive pedal. What the declaration does not indicate is that Asano was somehow so flawed that there was no reason to upgrade it, or pedals like it, to be compatible with modern engines. Indeed, Teleflex's own declarations refute this conclusion. Dr. Radcliffe states that Rixon suffered from the same bulk and complexity as did Asano. See *id.*, at 206. Teleflex's other expert,

however, explained that Rixon was itself designed by adding a sensor to a pre-existing mechanical pedal. See *id.*, at 209. If Rixon's base pedal was not too flawed to upgrade, then Dr. Radcliffe's declaration does not show Asano was either. Teleflex may have made a plausible argument that Asano is inefficient as compared to Engelgau's preferred embodiment, but to judge Asano against Engelgau would be to engage in the very hindsight bias Teleflex rightly urges must be avoided. Accordingly, Teleflex has not shown anything in the prior art that taught away from the use of Asano.

Like the District Court, finally, we conclude Teleflex has shown no secondary factors to dislodge the determination that claim 4 is obvious. Proper application of *Graham* and our other precedents to these facts therefore leads to the conclusion that claim 4 encompassed obvious subject matter. As a result, the claim fails to meet the requirement of § 103.

We need not reach the question whether the failure to disclose Asano during the prosecution of Engelgau voids the presumption of validity given to issued patents, for claim 4 is obvious despite the presumption. We nevertheless think it appropriate to note that the rationale underlying the presumption-that the PTO, in its expertise, has approved the claim-seems much diminished here.

IV

[8] A separate ground the Court of Appeals gave for reversing the order for summary judgment was the existence of a dispute over an issue of material fact. We disagree with the Court of Appeals on this point as well. To the extent the court understood the *Graham* approach to exclude the possibility of summary judgment when an expert provides a conclusory affidavit addressing the question of obviousness, it misunderstood the role expert testimony plays in the analysis. In considering summary judgment on that question the district court can and should take into account expert testimony, which may resolve or keep open certain questions of fact. That is not the end of the issue, however. The ultimate judgment of obviousness is a legal determination. *Graham*, 383 U.S., at 17, 86 S.Ct. 684. Where, as here, the content of the prior art, the scope of the patent ***1746** claim, and the level of ordinary skill in the art are not in material dispute, and the obviousness of the claim is apparent in light of these factors, summary judgment is appropriate. Nothing in the declarations proffered by Teleflex prevented the District Court from reaching the careful conclusions underlying its order for summary judgment in this case.

* * *

We build and create by bringing to the tangible and palpable reality around us new works based on instinct, simple logic, ordinary inferences, extraordinary ideas, and sometimes even genius. These advances, once part of our shared knowledge, define a new threshold from which innovation starts once more. And as progress beginning from higher levels of achievement is expected in the normal course, the results of ordinary innovation are not the subject of exclusive rights under the patent laws. Were it otherwise patents might stifle, rather than promote, the progress of useful arts. See U.S. Const., Art. I, § 8, cl. 8. These premises led to the bar on patents claiming obvious subject matter established in *Hotchkiss* and codified in § 103. Application of the bar must not be confined within a test or formulation too constrained to serve its purpose.

KSR provided convincing evidence that mounting a modular sensor on a fixed pivot point of the Asano pedal was a design step well within the grasp of a person of ordinary skill in the relevant art. Its arguments, and the record, demonstrate that claim 4 of the Engelgau patent is obvious. In rejecting the District Court's rulings, the Court of Appeals analyzed the issue in a narrow, rigid manner inconsistent with § 103 and our precedents. The judgment of the Court of Appeals is reversed, and the case remanded for further proceedings consistent with this

opinion.

It is so ordered.

U.S.,2007.
KSR Intern. Co. v. Teleflex Inc.
550 U.S. 398, 127 S.Ct. 1727, 167 L.Ed.2d 705, 75 USLW 4289, 82 U.S.P.Q.2d 1385, 07 Cal. Daily Op. Serv. 4654, 20 Fla. L. Weekly Fed. S 248

END OF DOCUMENT

Exhibit 4

Court of Appeals, Federal Circuit

In re O'Farrell

No. 87-1486

Decided August 10, 1988

PATENTS

1. Patentability/Validity — Obviousness — Evidence of (§115.0906)

Applicants' method of producing predetermined protein in stable form in host species of bacteria through genetic engineering is obvious within meaning of 35 USC 103 since reference, authored by two of three patent applicants and published more than one year prior to patent application date, contained detailed enabling methodology for practicing claimed invention, suggestion for modifying prior art to practice claimed invention, and evidence suggesting that invention could be successful, and reference thus rendered invention obvious to those of ordinary skill in art at time invention was made.

2. Patentability/Validity — Obviousness — Evidence of (§115.0906)

Experimenters' use of heterologous gene coded for ribosomal RNA, which is not ordinarily translated, rather than gene coded for predetermined protein, in plasmid cloning vector for introduction into host bacteria in genetic engineering experiment, does not require finding that applicant's claimed method of producing predetermined protein in host bacteria through genetic engineering was not obvious in view of published paper describing experiment, particularly observation that hybrid messenger RNA produced by experiment was apparently translated into protein, since it would have been obvious and reasonable to conclude from such observation that if gene coded for ribosomal RNA produced "junk" or "nonsense" protein, then use of gene coded for predetermined protein would result in production of "useful" protein, as application claims.

3. Patentability/Validity — Obviousness — In general (§115.0901)

Rejection of patent application cannot be overturned on ground that examiner and Board of Patent Appeals and Interferences applied impermissible "obvious to try" standard, since assignment of error for application of such standard usually occurs when invention is made by varying all parameters or trying each of numerous choices until successful without indication in prior art as to which parameters were critical or which choices were likely to be successful, or when invention is made by exploring promising new technology or general approach with only general guidance from prior art as to particular form of claimed invention or how to achieve it, and since neither situation is present in instant case.

4. Patentability/Validity — Obviousness — In general (§115.0901)

Finding of obviousness under 35 USC 103 requires only that prior art reveal reasonable expectation of success in producing claimed invention, rather than absolute prediction of such success.

Appeal from decision of Patent and Trademark Office, Board of Patent Appeals and Interferences.

Patent application, serial no. 180,424, filed by Patrick H. O'Farrell, Barry O. Polisky, and David H. Gelfand. From decision of Board of Patent Appeals and Interferences affirming final rejection of application on grounds of obviousness, applicants appeal. Affirmed.

J. Bruce McCubbrey of Fitch, Even, Tabin & Flannery (Virginia H. Meyer, with them on brief), San Francisco, Calif., for appellant.

Harris A. Pitlick, associate solicitor, Patent and Trademark Office (Joseph F. Nakamura, solicitor and Fred E. McKelvey, deputy solicitor, with him on brief), for appellee.

Before Markey, chief judge, and Rich and Nies, circuit judges.

Rich, J.

This appeal is from the decision of the United States Patent and Trademark Office Board of Patent Appeals and Interferences (board) affirming the patent examiner's final rejection of patent application Serial No. 180,424, entitled "Method and Hybrid Vector for Regulating Translation of heterologous DNA in Bacteria." The application was rejected under 35 USC 103 on the ground that the claimed invention would have been obvious at the time the invention was made in view of a published paper by two of the three coinventers, and a publication by Bahl, Marians & Wu 1 *Gene* 81 (1976) (Bahl). We affirm.

The claimed invention is from the developing new field of genetic engineering. A broad claim on appeal reads:

Claim 1. A method for producing a predetermined protein in a stable form in a transformed host species of bacteria comprising, providing a cloning vector which includes at least a substantial portion of a gene which is indigenous to the host species of bacteria and is functionally transcribed and translated in that species, said substantial portion of said indigenous gene further including the regulatory DNA sequences for RNA synthesis and protein synthesis but lacking the normal gene termination signal, and linking a natural or synthetic heterologous gene encoding said predetermined protein to said indigenous gene portion at its distal end, said heterologous gene being in proper orientation and having codons arranged in the same reading frame as the codons of said indigenous gene so that readthrough can occur from said indigenous gene portion into said heterologous gene in the same reading frame, said heterologous gene portion further containing sufficient DNA sequences to result in expression of a fused protein having sufficient size so as to confer stability on said predetermined protein when said vector is used to transform said host species of bacteria.

Illustrative embodiments are defined in more specific claims. For example:

Claim 2. A method for producing a predetermined protein in a stable form in a transformed host species of bacteria, comprising, providing an *E. coli* plasmid having an operator, a promoter, a site for the initiation of translation, and at least a substantial portion of the beta-galactosidase gene of the *E. coli* lactose operon, said substantial portion of said beta-galactosidase gene being under the control of said operator, promoter and site for initiation of translation, said substantial portion of said beta-galactosidase gene lacking the normal gene termination signal, and linking a heterologous gene encoding said predetermined protein to said beta-galactosidase gene portion at its distal end, said heterologous gene being in proper orientation and having codons arranged in the same reading frame as the codons of the said beta-galactosidase gene portion so that readthrough can occur from said beta-galactosidase gene portion into said heterologous gene in the same reading frame, said heterologous gene portion further containing sufficient DNA sequences to result in expression of a fused protein having sufficient size so as to confer stability on said predetermined protein when said vector is used to transform said host species of bacteria.

Claim 3. The method of Claim 2 wherein said *E. coli* plasmid comprises the plasmid designated pBGP120.

Although the terms in these claims would be familiar to those of ordinary skill in genetic engineering, they employ a bewildering vocabulary new to those who are not versed in molecular biology. An understanding of the science and technology on which these claims are based is essential before one can analyze and explain whether the claimed invention would have been obvious in light of the prior art.

I. *Background* [1]

Proteins are biological molecules of enormous importance. Proteins include enzymes that catalyze biochemical reactions, major structural materials of the animal body, and many hormones. Numerous patents and applications for patents in the field of biotechnology involve specific proteins or methods for making and using proteins. Many valuable proteins occur in nature only in minute quantities, or are difficult to purify from natural sources. Therefore, a goal of many biotechnology projects, including appellants' claimed invention, is to devise methods to synthesize useful quantities of specific proteins by controlling the mechanism by which living cells make proteins.

The basic organization of all proteins is the same. Proteins are large polymeric molecules consisting of chains of smaller building blocks, called *amino acids*, that are linked together covalently.[2] The chemical bonds linking amino acids together are called *peptide* bonds, so proteins are also called *poly-*

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[1] Basic background information about molecular biology and genetic engineering, can be found in Alberts, Bray, Lewis, Raff, Roberts & Watson, *The Molecular Biology of the Cell*, 1-253, 385-481 (1983) [hereinafter *The Cell*]; Watson, Hopkins, Roberts, Steitz & Weiner, *The Molecular Biology of the Gene*, Vol. 1 (4th ed., 1987) 3-502 [hereinafter *The Gene*]. These standard textbooks were used to supplement the information in the glossary supplied by appellants. The description here is necessarily simplified and omits important facts and concepts that are not necessary for the analysis of this case.

[2] There are twenty amino acids: alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan, glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine, aspartic acid, glutamic acid, lysine, arginine, and histidine.

peptides.[1] It is the exact sequence in which the amino acids are strung together in a polypeptide chain that determines the identity of a protein and its chemical characteristics.[2] Although there are only 20 amino acids, they are strung together in different orders to produce the hundreds of thousands of proteins found in nature.

To make a protein molecule, a cell needs information about the sequence in which the amino acids must be assembled. The cell uses a long polymeric molecule, DNA (deoxyribonucleic acid), to store this information. The subunits of the DNA chain are called *nucleotides*. A nucleotide consists of a nitrogen-containing ring compound (called a *base*) linked to a 5-carbon sugar that has a phosphate group attached.[3] DNA is composed of only four nucleotides. They differ from each other in the base region of the molecule. The four bases of these subunits are adenine, guanine, cytosine, and thymine (abbreviated respectively as A, G, C and T). The sequence of these bases along the DNA molecule specifies which amino acids will be inserted in sequence into the polypeptide chain of a protein.

DNA molecules do not participate directly in the synthesis of proteins. DNA acts as a permanent "blueprint" of all of the genetic information in the cell, and exists mainly in extremely long strands (called *chromosomes*) containing information coding for the sequences of many proteins, most of which are not being synthesized at any particular moment. The region of DNA on the chromosome that codes for the sequence of a single polypeptide is called a *gene*.[4] In order to *express* a gene (the process whereby the information in a gene is used to synthesize new protein), a copy of the gene is first made as a molecule of RNA (ribonucleic acid).

RNA is a molecule that closely resembles DNA. It differs, however in that it contains a different sugar (ribose instead of deoxyribose) and the base thymine (T) of DNA is replaced in RNA by the structurally similar base, uracil (U). Making an RNA copy of DNA is called *transcription*. The transcribed RNA copy contains sequences of A, U, C, and G that carry the same information as the sequence of A, T, C, and G in the DNA. That RNA molecule, called *messenger RNA*, then moves to a location in the cell where proteins are synthesized.

The code whereby a sequence of nucleotides along an RNA molecule is translated into a sequence of amino acids in a protein (i.e., the "genetic code") is based on serially reading groups of three adjacent nucleotides. Each combination of three adjacent nucleotides, called a *codon*, specifies a particular amino acid. For example, the codon U-G-G in a messenger RNA molecule specifies that there will be a tryptophan molecule in the corresponding location in the corresponding polypeptide. The four bases A, G, C and U can be combined as triplets in 64 different ways, but there are only 20 amino acids to be coded. Thus, most amino acids are coded for by more than one codon. For example, both U-A-U and U-A-C code for tyrosine, and there are six different codons that code for leucine. There are also three codons that do not code for any amino acid (namely, U-A-A, U-G-A, and U-A-G). Like periods at the end of a sentence, these sequences signal the end of the polypeptide chain, and they are therefore called *stop codons*.

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[1] Proteins are often loosely called *peptides*, but technically proteins are only the larger peptides with chains of at least 50 amino acids, and more typically hundreds of amino acids. Some proteins consist of several polypeptide chains bound together covalently or noncovalently. The term "peptide" is broader than "protein" and also includes small chains of amino acids linked by peptide bonds, some as small as two amino acids. Certain small peptides have commercial or medical significance.

[2] Polypeptide chains fold up into complex 3-dimensional shapes. It is the shape that actually determines many chemical properties of the protein. However, the configuration of a protein molecule is determined by its amino acid sequence. *The Cell* at 111-12; *The Gene* at 50-54.

[3] The sugar in DNA is deoxyribose, while the sugar in RNA, *infra*, is ribose. The sugar and phosphate groups are linked covalently to those of adjacent nucleotides to form the backbone of the long unbranched DNA molecule. The bases project from the chain, and serve as the "alphabet" of the genetic code.

DNA molecules actually consist of two chains tightly entwined as a double helix. The chains are not identical but instead are complementary: each A on one chain is paired with a T on the other chain, and each C has a corresponding G. The chains are held together by noncovalent bonds between these complementary bases. This double helical structure plays an essential role in the replication of DNA and the transmission of genetic information. *See generally The Cell* at 98-106; *The Gene* at 65-79. However, the information of only one strand is used for directing protein synthesis, and it is not necessary to discuss the implication of the double-stranded structure of DNA here. RNA molecules, *infra*, are single stranded.

[4] Chromosomes also contain regions of DNA that are not part of genes, i.e., do not code for the sequence of amino acids in proteins. These include sections of DNA adjacent to genes that are involved in the control of transcription, *infra*, and regions of unknown function.

The cellular machinery involved in synthesizing proteins is quite complicated, and centers around large structures called *ribosomes* that bind to the messenger RNA. The ribosomes and associated molecules "read" the information in the messenger RNA molecule, literally shifting along the strand of RNA three nucleotides at a time, adding the amino acid specified by that codon to a growing polypeptide chain that is also attached to the ribosome. When a stop codon is reached, the polypeptide chain is complete and detaches from the ribosome.

The conversion of the information from a sequence of codons in an RNA molecule into the sequence of amino acids in a newly synthesized polypeptide is called *translation*. A messenger RNA molecule is typically reused to make many copies of the same protein. Synthesis of a protein is usually terminated by destroying the messenger RNA. (The information for making more of that protein remains stored in DNA in the chromosomes.)

The translation of messenger RNA begins at a specific sequence of nucleotides that bind the RNA to the ribosome and specify which is the first codon that is to be translated. Translation then proceeds by reading nucleotides, three at a time, until a stop codon is reached. If some error were to occur that shifts the frame in which the nucleotides are read by one or two nucleotides, all of the codons after this shift would be misread. For example, the sequence of codons [. . .*C-U-C-A-G-C-G-U-U-A-C-C-A*. . .] codes for the chain of amino acids [. . .leucine-serine-valine-threonine-. . .]. If the reading of these groups of three nucleotides is displaced by one nucleotide, such as [. . .*C-U-C-A-G-C-G-U-U-A-C-C-A*. . .], the resulting peptide chain would consist of [. . .serine-alanine-leucine-proline. . .]. This would be an entirely different peptide, and most probably an undesirable and useless one. Synthesis of a particular protein requires that the correct register or *reading frame* be maintained as the codons in the RNA are translated.

The function of messenger RNA is to carry genetic information (transcribed from DNA) to the protein synthetic machinery of a cell where its information is translated into the amino acid sequence of a protein. However, some kinds of RNA have other roles. For example, ribosomes contain several large strands of RNA that serve a structural function (*ribosomal RNA*). Chromosomes contain regions of DNA that code for the nucleotide sequences of structural RNAs and these sequences are transcribed to manufacture those RNAs. The DNA sequences coding for structural RNAs are still called genes even though the nucleotide sequence of the structural RNA is never translated into protein.

Man, other animals, plants, protozoa, and yeast are *eucaryotic* (or eukaryotic) organisms: their DNA is packaged in chromosomes in a special compartment of the cell, the nucleus. Bacteria (*procaryotic* or prokaryotic organisms) have a different organization. Their DNA, usually a circular loop, is not contained in any specialized compartment. Despite the incredible differences between them, all organisms, whether eucaryote or procaryote, whether man or mouse or lowly bacterium, use the same molecular rules to make proteins under the control of genes. In all organisms, codons in DNA are transcribed into codons in RNA which is translated on ribosomes into polypeptides according to the same genetic code. Thus, if a gene from a man is transferred into a bacterium, the bacterium can manufacture the human protein. Since most commercially valuable proteins come from man or other eucaryotes while bacteria are essentially little biochemical factories that can be grown in huge quantities, one strategy for manufacturing a desired protein (for example, insulin) is to transfer the gene coding for the protein from the eucaryotic cell where the gene normally occurs into a bacterium.

Bacteria containing genes from a foreign source (*heterologous* genes) integrated into their own genetic makeup are said to be *transformed*. When transformed bacteria grow and divide, the inserted heterologous genes, like all the other genes that are normally present in the bacterium (*indigenous* genes), are replicated and passed on to succeeding generations. One can produce large quantities of transformed bacteria that contain transplanted heterologous genes. The process of making large quantities of identical copies of a gene (or other fragment of DNA) by introducing it into procaryotic cells and then growing those cells is called *cloning* the gene. After growing sufficient quantities of the transformed bacteria, the biotechnologist must induce the transformed bacteria to *express* the cloned gene and make useful quantities of the protein. This is the purpose of the claimed invention.

In order to make a selected protein by expressing its cloned gene in bacteria, several technical hurdles must be overcome. First the gene coding for the specific protein must be isolated for cloning. This is a formidable task, but recombinant DNA technology has armed the genetic engineer with a variety of

techniques to accomplish it.[7] Next the isolated gene must be introduced into the host bacterium. This can be done by incorporating the gene into a cloning vector. A *cloning vector* is a piece of DNA that can be introduced into bacteria and will then replicate itself as the bacterial cells grow and divide. Bacteriophage (viruses that infect bacteria) can be used as cloning vectors, but plasmids were the type used by appellants. A *plasmid* is a small circular loop of DNA found in bacteria, separate from the chromosome, that replicates like a chromosome. It is like a tiny auxilliary chromosome containing only a few genes. Because of their small size, plasmids are convenient for the molecular biologist to isolate and work with. Recombinant DNA technology can be used to modify plasmids by splicing in cloned eucaryotic genes and other useful segments of DNA containing control sequences. Short pieces of DNA can even be designed to have desired nucleotide sequences, synthesized chemically, and spliced into the plasmid. One use of such chemically synthesized linkers is to insure that the inserted gene has the same reading frame as the rest of the plasmid; this is a teaching of the Bahl reference cited against appellants. A plasmid constructed by the molecular geneticist can be inserted into bacteria, where it replicates as the bacteria grow.

Even after a cloned heterologous gene has been successfully inserted into bacteria using a plasmid as a cloning vector, and replicates as the bacteria grow, there is no guarantee that the gene will be expressed, i.e., transcribed and translated into protein. A bacterium such as *E. coli* (the species of bacterium used by appellants) has genes for several thousand proteins. At any given moment many of those genes are not expressed at all. The genetic engineer needs a method to "turn on" the cloned gene and force it to be expressed. This is the problem appellants worked to solve.

II. *Prior art*

Appellants sought to control the expression of cloned heterologous genes inserted into bacteria. They reported the results of their early efforts in a publication, the three authors of which included two of the three coinventor-appellants (the Polisky reference [8]), that is undisputed prior art against them. Their strategy was to link the foreign gene to a highly regulated indigenous gene. Turning on expression of the indigenous gene by normal control mechanisms of the host would cause expression of the linked heterologous gene.

As a controllable indigenous gene, the researchers chose a gene in the bacterium *E. coli* that makes beta-galactosidase. *Beta-galactosidase* is an enzyme needed to digest the sugar, lactose (milk sugar). When *E. coli* grows in a medium that contains no lactose, it does not make beta-galactosidase. If lactose is added to the medium, the gene coding for beta galactosidase is expressed. The bacterial cell makes beta-galactosidase and is then able to use lactose as a food source. When lactose is no longer available, the cell again stops expressing the gene for beta galactosidase.

The molecular mechanisms through which the presence of lactose turns on expression of the beta-galactosidase gene has been studied in detail, and is one of the best understood examples of how gene expression is regulated on the molecular level. The beta-galactosidase gene is controlled by segments of DNA adjacent to the gene. These *regulatory DNA sequences* (the general term used in Claim 1) include the *operator* and *promoter* sequences (specified in Claim 2).[9] The researchers constructed a plasmid containing the beta-galactosidase gene with its operator and promoter. This gene (with its regulatory sequences) was removed from the chromosome of *E. coli* where it is normally found and was transplanted to a plasmid that could be conveniently manipulated.

Restriction endonucleases are useful tools in genetic engineering. These enzymes cut strands of DNA, but only at places where a specific sequence of nucleotides is present. For example, one restriction endonuclease, called *EcoRI*, cuts DNA only at sites where

[7] See *The Cell* at 185–194; *The Gene* at 208–10.

[8] Polisky, Bishop & Gelfand, *A plasmid cloning vehicle allowing regulated expression of eukaryotic DNA in bacteria*, 73 Proc. Nat'l Acad. Sci. USA 3900 (1976).

[9] The *promoter* is a sequence of nucleotides where the enzyme that synthesizes RNA, *RNA polymerase*, attaches to the DNA to start the transcription of the beta-galactosidase gene. The *operator* is an overlapping DNA sequence that binds a small protein present in the cell, the lactose repressor protein. The lactose repressor protein binds to the operator and physically blocks the RNA polymerase from properly attaching to the promoter so that transcription cannot proceed. Lactose molecules interact with the lactose repressor protein and cause it to change its shape; after this change in shape it moves out of the way and no longer prevents the RNA polymerase from binding to the promoter. Messenger RNA coding for beta-galactosidase can then be transcribed. *See generally The Cell* at 438–39; *The Gene* at 474–80.

the nucleotide sequence is [. . .-G-A-A-T-T-C-. . .]. With restriction enzymes the genetic engineer can cut a strand of DNA at very specific sites into just a few pieces. With the help of "repair" enzymes, other pieces of DNA can be spliced onto the cut ends. The investigators found that the plasmid which they had constructed contained only two sequences that were cut by EcoRI. They were able to eliminate one of these sites that was unwanted. They were then left with a plasmid containing the beta-galactosidase gene with its regulatory sequences, and a single EcoRI site that was within the beta-galactosidase gene and close to its stop codon. They named this plasmid that they had constructed pBGP120.

The next step was to cut the plasmid open at its EcoRI site and insert a heterologous gene from another organism. The particular heterologous gene they chose to splice in was a segment of DNA from a frog that coded for ribosomal RNA. The frog gene was chosen as a test gene for reasons of convenience and availability. The new plasmid created by inserting the frog gene was similar to pBGP120, but its beta-galactosidase gene was incomplete. Some codons including the stop codon were missing from its end, which instead continued on with the sequence of the frog ribosomal RNA gene. The investigators named this new plasmid pBGP123. They inserted this plasmid back into *E. coli* and grew sufficient quantities for study. They then fed the *E. coli* with lactose. As they had intended, the lactose turned on transcription of the beta-galactosidase gene in the plasmid. RNA polymerase moved along the plasmid producing a strange new kind of RNA: Each long strand of RNA first contained codons for the messenger RNA for beta-galactosidase and then continued without interruption with the codons for the frog ribosomal RNA. Thus, there was *read-through* transcription in which the RNA polymerase first transcribed the indigenous (beta-galactosidase) gene and then "read through," i.e., continued into and through the adjacent heterologous (frog ribosomal RNA) gene. Although the RNA produced was a hybrid, it nevertheless contained a nucleotide sequence dictated by DNA from a frog. The researchers had achieved the first controlled transcription of an animal gene inside a bacterium.

The researchers had used a gene coding for a ribosomal RNA as their heterologous test gene. Ribosomal RNA is not normally translated into protein. Nevertheless, they were obviously interested in using their approach to make heterologous proteins in bacteria. They therefore examined the beta-galactosidase made by their transformed bacteria. Patrick O'Farrell, who was not a coauthor of the Polisky paper but was to become a coinventor in the patent application, joined as a collaborator. They found that beta-galactosidase from the transformed bacteria had a higher molecular weight than was normal. They concluded that the bacteria must have used their strange new hybrid RNA like any other messenger RNA and translated it into protein. When the machinery of protein synthesis reached the premature end of the sequence coding for beta-galactosidase it continued right on, three nucleotides at a time, adding whatever amino acid was coded for by those nucleotides, until a triplet was reached with the sequence of a stop codon. The resulting polypeptide chains had more amino acids than normal beta-galactosidase, and thus a higher molecular weight. The researchers published their preliminary results in the Polisky article. They wrote:

> [I]f the normal translational stop signals for [beta]-galactosidase are missing in pBGP120, in-phase translational read-through into adjacent inserted sequences might occur, resulting in a significant increase in the size of the [beta]-galactosidase polypeptide subunit. In fact, we have recently observed that induced cultures of pBGP123 contain elevated levels of [beta]-galactosidase of higher subunit molecular weight than wild-type enzyme (P. O'Farrell, unpublished experiments). We believe this increase results from translation of *Xenopus* [frog] RNA sequences covalently linked to [messenger] RNA for [beta]-galactosidase, resulting in a fused polypeptide.

Polisky at 3904.

Since ribosomal RNA is never translated in normal cells, the polypeptide chain produced by translating that chain was not a naturally occurring, identified protein. The authors of the Polisky paper explicitly pointed out that if one were to insert a heterologous gene coding for a protein into their plasmid, it should produce a "fused protein" consisting of a polypeptide made of beta-galactosidase plus the protein coded for by the inserted gene, joined by a peptide bond into a single continuous polypeptide chain:

> It would be interesting to examine the expression of a normally translated eukaryotic sequence in pBGP120. If an inserted sequence contains a ribosome binding site that can be utilized in bacteria, production of high levels of a readthrough transcript might allow for extensive translation of a functional eukaryotic polypeptide. In the absence of an independent ribosome bind-

ing site, the eukaryotic sequence would be translated to yield a peptide covalently linked to [beta]-galactosidase. The extent of readthrough translation under *lac* control will depend on the number of translatable codons between the EcoRI site and the first in-phase nonsense [i.e., stop] codon in the inserted sequence.

Id.

III. *The Claimed Invention*

Referring back to Claims 1 through 3, it can be seen that virtually everything in the claims was present in the prior art Polisky article. The main difference is that in Polisky the heterologous gene was a gene for ribosomal RNA while the claimed invention substitutes a gene coding for a predetermined protein. Ribosomal RNA gene is not normally translated into protein, so expression of the heterologous gene was studied mainly in terms of transcription into RNA. Nevertheless, Polisky mentioned preliminary evidence that the transcript of the ribosomal RNA gene was translated into protein. Polisky further predicted that if a gene that codes for a protein were to be substituted for the ribosomal RNA gene, "a readthrough transcript might allow for extensive translation of a functional eukaryotic polypeptide." Thus, the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the method could be used to make proteins.

Appellants reduced their invention to practice some time in 1976 and reported their results in a paper that was published in 1978.[10] During 1977 they communicated their results to another group of researchers who used the readthrough translation approach to achieve the first synthesis of a human protein in bacteria.[11] Appellants filed an application to patent their invention on August 9, 1978, of which the application on appeal is a division.

IV. *The Obviousness Rejection*

The application was rejected under 35 USC 103. The position of the examiner and the Board is, simply, that so much of the appellant's method was revealed in the Polisky reference that making a protein by substituting its gene for the ribosomal RNA gene in Polisky (as suggested by Polisky) would have been obvious to one of ordinary skill in the art at the time that the invention was made.

The claims specify that the heterologous gene should be inserted into the plasmid in the same orientation and with the same reading frame as the preceding portion of the indigenous gene. In view of this limitation, the §103 rejection was based either on Polisky alone (supplemented by the fact that the importance of orientation and reading frame was well known in the prior art) or in combination with the Bahl reference which describes a general method for inserting a piece of chemically synthesized DNA into a plasmid. Bahl teaches that this technique could be used to shift the sequence of DNA inserted into a plasmid into the proper reading frame.

Appellants argue that at the time the Polisky article was published, there was significant unpredictability in the field of molecular biology so that the Polisky article would not have rendered the claimed method obvious to one of ordinary skill in the art. Even though there was speculation in the article that genes coding for proteins could be substituted for the ribosomal RNA gene and would be expressed as readthrough translation into the protein, this had never been done. Appellants say that it was not yet certain whether a heterologous protein could actually be produced in bacteria, and if it could, whether additional mechanisms or methods would be required. They contend

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[10] O'Farrell, Polisk & Gelfand, *Regulated expression by readthrough translation from a plasmid-encoded beta-galactosidase*, 134 J. Bacteriol. 645 (1978). The heterologous genes expressed in these studies were not predetermined, but were instead unidentified genes of unknown origin. The authors speculated that they were probably genes from *E. coli* that were contaminants in the source of beta-galactosidase genes. *Id.* at 648

[11] Itakura, Hirose, Crea, Riggs, Heynecker, Bolivar & Boyer, *Expression in Escherichia coli of a chemically synthesized gene for the hormone samatostatin*, 198 Science 1056 (1977). A pioneering accomplishment of the Itakura group is that the gene was not from a human source, but instead was entirely synthesized in the laboratory using chemical methods. It is not clear whether the appellants communicated only the results reported in the Polisky publication or whether they communicated the complete claimed invention.

that without such certainty the predictions in the Polisky paper, which hindsight now shows to have been correct, were merely invitations to those skilled in the art to try to make the claimed invention. They argue that the rejection amounts to the application of a standard of "obvious to try" to the field of molecular biology, a standard which this court and its predecessors have repeatedly rejected as improper grounds for a §103 rejection. *E.g., In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988); *In re Geiger*, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987); *In re Merck & Co., Inc.*, 800 F.2d 1091, 1097, 231 USPQ 375, 379 (Fed. Cir. 1986); *In re Antonie*, 559 F.2d 618, 620, 195 USPQ 6, 8 (CCPA 1977).

Obviousness under §103 is a question of law. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568, 1 USPQ2d 1593, 1597 (Fed. Cir.), *cert. denied*, 107 S.Ct. 2187 (1987). An analysis of obviousness must be based on several factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). *See, e.g., Custom Accessories, Inc. v. Jeffrey-Allan Indus.*, 807 F.2d 955, 958, 1 USPQ2d 1196, 1197 (Fed. Cir. 1986). The scope and content of the prior art and the differences between the prior art and the claimed invention have been examined in sections II and III, *supra*. Appellants say that in 1976 those of ordinary skill in the arts of molecular biology and recombinant DNA technology were research scientists who had "extraordinary skill in relevant arts" and "were among the brightest biologists in the world." Objective evidence of nonobviousness was not argued.

[1] With the statutory factors as expounded by *Graham* in mind and considering all of the evidence, this court must determine the correctness of the board's legal determination that the claimed invention as a whole would have been obvious to a person having ordinary skill in the art at the time the invention was made. We agree with the board that appellants' claimed invention would have been obvious in light of the Polisky reference alone or in combination with Bahl within the meaning of §103. Polisky contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.

[2] Appellants argue that after the publication of Polisky, successful synthesis of protein was still uncertain. They belittle the predictive value of the observation that expression of the transcribed RNA in Polisky produced beta-galactosidase with a greater than normal molecular weight, arguing that since ribosomal RNA is not normally translated, the polypeptide chains that were added to the end of the beta-galactosidase were "junk" or "nonsense" proteins. This characterization ignores the clear implications of the reported observations. The Polisky study directly proved that a readthrough transcript messenger RNA had been produced. The preliminary observation showed that this messenger RNA was read and used for successful translation. It was well known in the art that ribosomal RNA was made of the same nucleotides as messenger RNA, that any sequence of nucleotides could be read in groups of three as codons, and that reading these codons should specify a polypeptide chain that would elongate until a stop codon was encountered. The preliminary observations thus showed that codons beyond the end of the beta-galactosidase gene were being translated into peptide chains. This would reasonably suggest to one skilled in the art that if the codons inserted beyond the end of the beta-galactosidase gene coded for a "predetermined protein," that protein would be produced. In other words, it would have been obvious and reasonable to conclude from the observation reported in Polisky that since nonsense RNA produced nonsense polypeptides, if meaningful RNA was inserted instead of ribosomal RNA, useful protein would be the result. The relative shortness of the added chains is also not a source of uncertainty, since one skilled in the art would have known that a random sequence of nucleotides would produce a stop codon before the chain got too long.[12]

Appellants complain that since predetermined proteins had not yet been produced in transformed bacteria, there was uncertainty as to whether this could be done, and that the rejection is thus founded on an impermissible "obvious to try" standard. It is true that this court and its predecessors have repeatedly emphasized that "obvious to try" is not the standard under §103. However, the meaning of this maxim is sometime lost. Any invention that would in fact have been obvious under §103 would also have been, in a sense, obvious to try. The question is: when is an

[12] The patent application indicates that chains as long as 60 amino acids were added, which is hardly a trivial length of polypeptide.

invention that was obvious to try nevertheless nonobvious?

[3] The admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. *E.g., In re Geiger*, 815 F.2d at 688, 2 USPQ2d at 1278; *Novo Industri A/S v. Travenol Laboratories, Inc.*, 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); *In re Yates*, 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); *In re Antonie*, 559 F.2d at 621, 195 USPQ at 8-9. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. *In re Dow Chemical Co.*, 837 F.2d, 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1985); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380, 231 USFQ 81, 90-91 (Fed. Cir. 1986), *cert. denied*, 107 S.Ct. 1606 (1987); *In re Tomlinson*, 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966). Neither of these situations applies here.

[4] Obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious. *In re Merck & Co.*, 800 F.2d at 1098, 231 USPQ at 380; *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1461, 221 USPQ 481, 488 (Fed. Cir. 1984); *In re Papesch*, 315 F.2d 381, 386-87, 137 USPQ 43, 47-48 (CCPA 1963). For obviousness under §103, all that is required is a reasonable expectation of success. *In re Longi*, 759 F.2d 887, 897, 225 USPQ 645, 651-52 (Fed. Cir. 1985); *In re Clinton*, 527 F.2d 1226, 1228, 188 USPQ 365, 367 (CCPA 1976). The information in the Polisky reference, when combined with the Bahl reference provided such a reasonable expectation of success.

Appellants published their pioneering studies of the expression of frog ribosomal RNA genes in bacteria more than a year before they applied for a patent. After providing virtually all of their method to the public without applying for a patent within a year, they foreclosed themselves from obtaining a patent on a method that would have been obvious from their publication to those of ordinary skill in the art, with or without the disclosures of other prior art. The decision of the board is

AFFIRMED.

District Court, W.D. Washington

Specialized Electronics Corp. v. Aviation Supplies & Academics Inc.

No. C86-712D

Decided March 23, 1988

PATENTS

1. Patentability/Validity — Obviousness — Secondary considerations (§115.0907)

Patent infringement defendant has failed to sustain its burden of proving, by clear and convincing evidence, that claims for hand-held aircraft navigational computers are invalid for obviousness under 35 USC 103, in view of objective evidence of secondary considerations demonstrating non-obviousness.

2. Infringement — Defenses — Prosecution history estoppel (§120.1105)

Doctrine of prosecution history estoppel applies to arguments narrowing construction of claims even if claims are not amended.

3. Patent construction — Claims — Broad or narrow (§125.1303)

Doctrine of claim differentiation precludes reading into independent claim limitation explicitly set forth in another claim, and such doctrine, although it is useful tool of claim construction, cannot be used to repudiate arguments made to Patent and Trademark Office in order to obtain allowance of asserted claims over prior art.

Particular patents — General and mechanical — Computers

3,979,057, Katz, Aronson, and Turek, self-contained hand-held electronic computer for aircraft navigation problems, claim 27 valid but not infringed.

3,979,058, Katz, Aronson, and Turek, self-contained electronic computer for math-

Exhibit 5

2143.02 Reasonable Expectation of Success Is Required [R-6] - 2100 Patentability

2143.02 Reasonable Expectation of Success Is Required [R-6]

>A rationale to support a conclusion that a claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1395 (2007); *Sakraida v. AG Pro, Inc.*, 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); *Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp.*, 340 U.S. 147, 152, 87 USPQ 303, 306 (1950).

I. < OBVIOUSNESS REQUIRES ONLY A REASONABLE EXPECTATION OF SUCCESS

The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) (Claims directed to a method of treating depression with amitriptyline (or nontoxic salts thereof) were rejected as *prima facie* obvious over prior art disclosures that amitriptyline is a compound known to possess psychotropic properties and that imipramine is a structurally similar psychotropic compound known to possess antidepressive properties, in view of prior art suggesting the aforementioned compounds would be expected to have similar activity because the structural difference between the compounds involves a known bioisosteric replacement and because a research paper comparing the pharmacological properties of these two compounds suggested clinical testing of amitriptyline as an antidepressant. The court sustained the rejection, finding that the teachings of the prior art provide a sufficient basis for a reasonable expectation of success.); *Ex parte Blanc*, 13 USPQ2d 1383 (Bd. Pat. App. & Inter. 1989) (Claims were directed to a process of sterilizing a polyolefinic composition with high-energy radiation in the presence of a phenolic polyester antioxidant to inhibit discoloration or degradation of the polyolefin. Appellant argued that it is unpredictable whether a particular antioxidant will solve the problem of discoloration or degradation. However, the Board found that because the prior art taught that appellant's preferred antioxidant is very efficient and provides better

results compared with other prior art antioxidants, there would have been a reasonable expectation of success.).

>II. < AT LEAST SOME DEGREE OF PREDICTABILITY IS REQUIRED; APPLICANTS MAY PRESENT EVIDENCE SHOWING THERE WAS NO REASONABLE EXPECTATION OF SUCCESS

Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) (Claims directed to a method for the commercial scale production of polyesters in the presence of a solvent at superatmospheric pressure were rejected as obvious over a reference which taught the claimed method at atmospheric pressure in view of a reference which taught the claimed process except for the presence of a solvent. The court reversed, finding there was no reasonable expectation that a process combining the prior art steps could be successfully scaled up in view of unchallenged evidence showing that the prior art processes individually could not be commercially scaled up successfully.). See also *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1207-08, 18 USPQ2d 1016, 1022-23 (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991) (In the context of a biotechnology case, testimony supported the conclusion that the references did not show that there was a reasonable expectation of success.); *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.).

>III. < PREDICTABILITY IS DETERMINED AT THE TIME THE INVENTION WAS MADE

Whether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. *Ex parte Erlich*, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986) (Although an earlier case reversed a rejection because of unpredictability in the field of monoclonal antibodies, the court found "in this case at the time this invention was made, one of ordinary skill in the art would have been motivated to produce monoclonal antibodies specific for human fibroplast interferon using the method of [the prior art] with a reasonable expectation of success." 3 USPQ2d at 1016 (emphasis in original).).

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Exhibit 6

United States Court of Appeals,
Federal Circuit.
In re Mark A. VAECK, Wipa Chungjatupornchai and Lee McIntosh.
No. 91-1120.

Oct. 21, 1991.

Inventor sought patent for claimed invention directed to use of genetic engineering techniques for production of insecticidal proteins. The United States Patent and Trademark Office Board of Patent Appeals and Interferences affirmed an examiner's rejection of certain claims, and appeal was taken. The Court of Appeals, Rich, Circuit Judge, held that: (1) patent application was improperly rejected on ground of prima facie obviousness, and (2) patent application was properly rejected to extent that claims were too general to enable person skilled in art to make and use claimed invention without undue experimentation.

Affirmed in part, reversed in part.

Mayer, Circuit Judge, dissented and filed opinion.

West Headnotes

[1] Patents 291 ⇐314(5)

291 Patents
291XII Infringement
291XII(C) Suits in Equity
291k314 Hearing
291k314(5) k. Questions of Law or Fact. Most Cited Cases
Obviousness of invention for which patent is sought is legal question which court independently reviews, though based upon Patent and Trademark Office's underlying factual findings, which court reviews under clearly erroneous standard. 35 U.S.C.A. § 103.

[2] Patents 291 ⇐16(2)

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16 Invention and Obviousness in General
291k16(2) k. Prior Art in General. Most Cited Cases
In reviewing rejection of invention for patent as obvious in view of combination of prior art references, court considers whether prior art would have suggested to those of ordinary skill in art that they should make claimed composition or device, or carry out claimed process, and whether prior art would also have revealed that in so making or carrying out, those of ordinary skill would have reasonable expectation of success; both suggestion and reasonable expectation of success must be found in prior art, not in applicant's disclosure. 35 U.S.C.A. § 103.

[3] Patents 291 ⇐16.25

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.25 k. Chemical Compounds. Most Cited Cases
Patent application for genetic engineering techniques for production of insecticidal proteins was improperly rejected on ground of prima facie obviousness; prior art did not disclose or suggest expression in cyanobacteria of chimeric gene encoding insecticidally active protein, or convey to those of ordinary skill reasonable expectation of success in doing so. 35 U.S.C.A. § 103.

[4] Patents 291 ⇐99

291 Patents
291IV Applications and Proceedings Thereon
291k99 k. Description of Invention in Specification. Most Cited Cases
To be patentable, specification of patent must enable any person skilled in art to which it pertains to

make and use claimed invention without undue experimentation. 35 U.S.C.A. § 112.

[5] Patents 291 ⇐99

291 Patents
291IV Applications and Proceedings Thereon
291k99 k. Description of Invention in Specification. Most Cited Cases
Patent application for using genetic engineering techniques to produce insecticidal proteins was properly rejected to extent that claims were too general to enable person skilled in art to make and use claimed invention without undue experimentation; claim referred to use of cyanobacteria in general as host organism, despite fact that cyanobacteria were diverse and relatively poorly studied group of organisms, comprising some 150 different genera, with successful use of any one type in manner called for in invention being unpredictable. 35 U.S.C.A. § 112.

[6] Patents 291 ⇐99

291 Patents
291IV Applications and Proceedings Thereon
291k99 k. Description of Invention in Specification. Most Cited Cases
Although patent applicants are not required to disclose every species encompassed by their claims, even in unpredictable art, in order to satisfy enablement requirement for patentability, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use invention as broadly as it is claimed. 35 U.S.C.A. § 112.

Patents 291 ⇐328(2)

291 Patents
291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents
291k328 Patents Enumerated
291k328(2) k. Original Utility. Most Cited Cases
4,695,455. Cited.

***489** Ian C. McLeod,Ian C. McLeod, P.C., Okemos, Mich., argued for appellant.

Teddy S. Gron, Associate Sol., Office of the Sol., of Arlington, Va., argued for appellee. With him on the brief were Fred E. McKelvey, Sol. and Richard E. Schafer, Associate Sol.

Before RICH, ARCHER, and MAYER, Circuit Judges.

RICH, Circuit Judge.

This appeal is from the September 12, 1990 decision of the Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board), affirming the examiner's rejection of claims 1-48 and 50-52 of application Serial No. 07/021,405, filed March 4, 1987, titled "Hybrid Genes Incorporating a DNA Fragment Containing a Gene Coding for an Insecticidal Protein, Plasmids, Transformed Cyanobacteria Expressing Such Protein and Method for Use as a Biocontrol Agent" as unpatentable under 35 U.S.C. § 103, as well as the rejection of claims 1-48 and 50-51 under 35 U.S.C. § 112, first paragraph, for lack of enablement. We reverse the § 103 rejection. The § 112 rejection is affirmed in part and reversed in part.

BACKGROUND

A. The Invention

The claimed invention is directed to the use of genetic engineering techniques [FN1] for production of proteins that are toxic to insects such as larvae of mosquitos and black flies. These swamp-dwelling pests are the source of numerous human health problems, including malaria. It is known that certain species of the naturally-occurring *Bacillus* genus of bacteria produce proteins ("endotoxins") that are toxic to these insects. Prior art methods of combatting the insects involved spreading or spraying crystalline spores of the insecticidal *Bacillus*

proteins over swamps. The spores were environmentally unstable, however, and would often sink to the bottom of a swamp before being consumed, thus rendering this method prohibitively expensive. Hence the need for a lower-cost method of producing the insecticidal *Bacillus* proteins in high volume, with application in a more stable vehicle.

FN1. Basic vocabulary and techniques for gene cloning and expression have been described in *In re O'Farrell,* 853 F.2d 894, 895-99, 7 U.S.P.Q.2d 1673, 1674-77 (Fed.Cir.1988), and are not repeated here.

As described by appellants, the claimed subject matter meets this need by providing for the production of the insecticidal *Bacillus* proteins within host cyanobacteria. Although both cyanobacteria and bacteria are members of the procaryote [FN2] kingdom, the cyanobacteria (which in the past have been referred to as "blue-green algae") are unique among procaryotes in that the cyanobacteria are capable of oxygenic photosynthesis. The cyanobacteria grow on top of swamps where they are consumed by mosquitos and black flies. Thus, when *Bacillus* proteins are produced within***490** transformed [FN3] cyanobacterial hosts according to the claimed invention, the presence of the insecticide in the food of the targeted insects advantageously guarantees direct uptake by the insects.

FN2. All living cells can be classified into one of two broad groups, procaryotes and eucaryotes. The procaryotes comprise organisms formed of cells that do not have a distinct nucleus; their DNA floats throughout the cellular cytoplasm. In contrast, the cells of eucaryotic organisms such as man, other animals, plants, protozoa, algae and yeast have a distinct nucleus wherein their DNA resides.

FN3. "Transformed" cyanobacteria are those that have successfully taken up the foreign *Bacillus* DNA such that the DNA information has become a permanent part of the host cyanobacteria, to be replicated as new cyanobacteria are generated.

More particularly, the subject matter of the application on appeal includes a chimeric (i.e., hybrid) gene comprising (1) a gene derived from a bacterium of the *Bacillus* genus whose product is an insecticidal protein, united with (2) a DNA promoter effective for expressing [FN4] the *Bacillus* gene in a host cyanobacterium, so as to produce the desired insecticidal protein.

FN4. "Expression" of a gene refers to the production of the protein which the gene encodes; more specifically, it is the process of transferring information from a gene (which consists of DNA) via messenger RNA to ribosomes where a specific protein is made.

The claims on appeal are 1-48 and 50-52, all claims remaining in the application. Claim 1 reads:

1. A chimeric gene capable of being expressed in Cyanobacteria cells comprising:

(a) a DNA fragment comprising a promoter region which is effective for expression of a DNA fragment in a Cyanobacterium; and

(b) at least one DNA fragment coding for an insecticidally active protein produced by a Bacillus strain, or coding for an insecticidally active truncated form of the above protein or coding for a protein having substantial sequence homology to the active protein,

the DNA fragments being linked so that the gene is expressed.

Claims 2-15, which depend from claim 1, recite preferred *Bacillus* species, promoters, and selectable markers.[FN5] Independent claim 16 and claims 17-31 which depend therefrom are directed to a hybrid plasmid vector which includes the chimeric gene of claim 1. Claim 32 recites a bacterial strain. Independent claim 33 and claims 34-48 which depend therefrom recite a cyanobacterium which ex-

presses the chimeric gene of claim 1. Claims 50-51 recite an insecticidal composition. Claim 52 recites a particular plasmid that appellants have deposited.

> FN5. In the context of the claimed invention, "selectable markers" or "marker genes" refer to antibiotic-resistance conferring DNA fragments, attached to the gene being expressed, which facilitate the selection of successfully transformed cyanobacteria.

B. Appellants' Disclosure

In addition to describing the claimed invention in generic terms, appellants' specification discloses two particular species of *Bacillus* (*B. thuringiensis, B. sphaericus*) as sources of insecticidal protein; and nine genera of cyanobacteria (*Synechocystis, Anacystis, Synechococcus, Agmenellum, Aphanocapsa, Gloecapsa, Nostoc, Anabaena* and *Ffremyllia*) as useful hosts.

The working examples relevant to the claims on appeal detail the transformation of a single strain of cyanobacteria, i.e., *Synechocystis* 6803. In one example, *Synechocystis* 6803 cells are transformed with a plasmid comprising (1) a gene encoding a particular insecticidal protein ("B.t. 8") from *Bacillus thuringiensis* var. *israelensis,* linked to (2) a particular promoter, the P_L promoter from the bacteriophage Lambda (a virus of *E. coli*). In another example, a different promoter, i.e., the *Synechocystis* 6803 promoter for the rubisco operon, is utilized instead of the Lambda P_L promoter.

C. The Prior Art

A total of eleven prior art references were cited and applied, in various combinations, against the claims on appeal.

The focus of Dzelzkalns,[FN6] the primary reference cited against all of the rejected claims, is to determine whether chloroplast promoter sequences can function in cyanobacteria. To that end Dzelzkalns discloses the expression in cyanobacteria of a chimeric gene comprising a chloroplast promoter***491** sequence fused to a gene encoding the enzyme chloramphenicol acetyl transferase (CAT).[FN7] Importantly, Dzelzkalns teaches the use of the CAT gene as a "marker" gene; this use of antibiotic resistance-conferring genes for selection purposes is a common technique in genetic engineering.

> FN6. 12 *Nucleic Acids Res.* 8917 (1984).

> FN7. Chloramphenicol is an antibiotic; CAT is an enzyme which destroys chloramphenicol and thus imparts resistance thereto.

Sekar I,[FN8] Sekar II,[FN9] and Ganesan [FN10] collectively disclose expression of genes encoding certain *Bacillus* insecticidal proteins in the bacterial hosts *B. megaterium, B. subtilis* and *E. coli.*

> FN8. 137 *Biochem. and Biophys. Res. Comm.* 748 (1986).

> FN9. 33 *Gene* 151 (1985).

> FN10. 189 *Mol. Gen. Genet.* 181 (1983).

Friedberg [FN11] discloses the transformation of the cyanobacterium *Anacystis nidulans* R2 by a plasmid vector comprising the O_LP_L operator-promoter region and a temperature-sensitive repressor gene of the bacteriophage Lambda. While the cyanobacteria are attractive organisms for the cloning of genes involved in photosynthesis, Friedberg states, problems may still be encountered such as suboptimal expression of the cloned gene, detrimental effects on cell growth of overexpressed, highly hydrophobic proteins, and rapid turnover of some gene products. To address these problems, Friedberg teaches the use of the disclosed Lambda regulatory signals in plasmid vehicles which, it states, have "considerable potential for use as vectors the expression of which can be controlled in *Anacystis....*"

FN11. 203 *Mol. Gen. Genet.* 505 (1986).

Miller [FN12] compares the initiation specificities *in vitro* of DNA-dependent RNA polymerases [FN13] purified from two different species of cyanobacteria (*Fremyella diplosiphon* and *Anacystis nidulans*), as well as from *E. coli.*

FN12. 140 *J. Bacteriology* 246 (1979).

FN13. RNA polymerase, the enzyme responsible for making RNA from DNA, binds at specific nucleotide sequences (promoters) in front of genes in DNA, and then moves through the gene making an RNA molecule that includes the information contained in the gene. Initiation specificity is the ability of the RNA polymerase to initiate this process specifically at a site(s) on the DNA template.

Nierzwicki-Bauer [FN14] identifies in the cyanobacterium *Anabaena* 7120 the start site for transcription of the gene encoding *rbcL,* the large subunit of the enzyme ribulose-1,5-bisphosphate carboxylase. It reports that the nucleotide sequence 14-8 base pairs preceding the transcription start site "resembles a good *Escherichia coli* promoter," but that the sequence 35 base pairs before the start site does not.

FN14. 81 *Proc. Natl. Acad. Sci. USA* 5961 (1984).

Chauvat [FN15] discloses host-vector systems for gene cloning in the cyanobacterium *Synechocystis* 6803, in which the antibiotic resistance-conferring *neo* gene is utilized as a selectable marker.

FN15. 204 *Mol. Gen. Genet.* 185 (1986).

Reiss [FN16] studies expression in *E. coli* of various proteins formed by fusion of certain foreign DNA sequences with the *neo* gene.

FN16. 30 *Gene* 211 (1984).

Kolowsky [FN17] discloses chimeric plasmids designed for transformation of the cyanobacterium *Synechococcus* R2, comprising an antibiotic-resistant gene linked to chromosomal DNA from the *Synechococcus* cyanobacterium.

FN17. 27 *Gene* 289 (1984).

Barnes, United States Patent No. 4,695,455, is directed to the treatment with stabilizing chemical reagents of pesticides produced by expression of heterologous genes (such as those encoding *Bacillus* proteins) in host microbial cells such as *Pseudomonas* bacteria. The host cells are killed by this treatment, but the resulting pesticidal compositions exhibit prolonged toxic activity when exposed to the environment of target pests.

***492** *D. The Grounds of Rejection*

1. The § 103 Rejections

Claims 1-6, 16-21, 33-38, 47-48 and 52 (which include all independent claims in the application) were rejected as unpatentable under 35 U.S.C. § 103 based upon Dzelzkalns in view of Sekar I or Sekar II and Ganesan. The examiner stated that Dzelzkalns discloses a chimeric gene capable of being highly expressed in a cyanobacterium, said gene comprising a promoter region effective for expression in a cyanobacterium operably linked to a structural gene encoding CAT. The examiner acknowledged that the chimeric gene and transformed host of Dzelzkalns differ from the claimed invention in that the former's structural gene encodes CAT rather than insecticidally active protein. However, the examiner pointed out, Sekar I, Sekar II, and Ganesan teach genes encoding insecticidally active proteins produced by *Bacillus,* and the advantages of expressing such genes in heterologous [FN18] hosts to obtain larger quantities of the protein. The examiner contended that it would have been obvious to one of ordinary skill in the art to substitute the *Bacillus* genes taught by Sekar I, Sekar II, and Ganesan for the CAT gene in the vec-

tors of Dzelzkalns in order to obtain high level expression of the *Bacillus* genes in the transformed cyanobacteria. The examiner further contended that it would have been obvious to use cyanobacteria as heterologous hosts for expression of the claimed genes due to the ability of cyanobacteria to serve as transformed hosts for the expression of heterologous genes. In the absence of evidence to the contrary, the examiner contended, the invention as a whole was prima facie obvious.

> FN18. Denotes different species or organism.

Additional rejections were entered against various groups of dependent claims which we need not address here. All additional rejections were made in view of Dzelzkalns in combination with Sekar I, Sekar II, and Ganesan, and further in view of other references discussed in Part C above.

The Board affirmed the § 103 rejections, basically adopting the examiner's Answer as its opinion while adding a few comments. The legal conclusion of obviousness does not require absolute certainty, the Board added, but only a reasonable expectation of success, citing *In re O'Farrell,* 853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed.Cir.1988). In view of the disclosures of the prior art, the Board concluded, one of ordinary skill in the art would have been motivated by a reasonable expectation of success to make the substitution suggested by the examiner.

2. The § 112 Rejection

The examiner also rejected claims 1-48 and 50-51 under 35 U.S.C. § 112, first paragraph, on the ground that the disclosure was enabling only for claims limited in accordance with the specification as filed. Citing *Manual of Patent Examining Procedure* (MPEP) provisions 706.03(n) [FN19] and (z) [FN20] as support, the examiner took the position that undue experimentation would be required of the art worker to practice the claimed invention, in view of the unpredictability in the art, the breadth of the claims, the limited number of working examples and the limited guidance provided ***493** in the specification. With respect to unpredictability, the examiner stated that

> FN19. MPEP 706.03(n), "Correspondence of Claim and Disclosure," provides in part:
>
> > In chemical cases, a claim may be so broad as to not be supported by [the] disclosure, in which case it is rejected as unwarranted by the disclosure....
>
> FN20. MPEP 706.03(z), "Undue Breadth," provides in part:
>
> > [I]n applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Sol,* 1938 C.D. 723; 497 O.G. 546. This is because in arts such as chemistry it is not obvious from the disclosure of one species, what other species will work. *In re Dreshfield,* 1940 C.D. 351; 518 O.G. 255 gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." ...

[t]he cyanobacteria comprise a large and diverse group of photosynthetic bacteria including large numbers of species in some 150 different genera including *Synechocystis, Anacystis, Synechococcus, Agmenellum, Nostoc, Anabaena,* etc. The molecular biology of these organisms has only recently become the subject of intensive investigation and this work is limited to a few genera.

> Therefore the level of unpredictability regarding heterologous gene expression in this large, diverse and relatively poorly studied group of procaryotes is high....

The Board affirmed, noting that "the limited guidance in the specification, considered in light of the relatively high degree of unpredictability in this particular art, would not have enabled one having ordinary skill in the art to practice the broad scope of the claimed invention without undue experimentation. *In re Fisher,* 427 F.2d 833, 166 U.S.P.Q. 18 (CCPA 1970)."

OPINION

A. *Obviousness*

[1] We first address whether the PTO erred in rejecting the claims on appeal as prima facie obvious within the meaning of 35 U.S.C. § 103. Obviousness is a legal question which this court independently reviews, though based upon underlying factual findings which we review under the clearly erroneous standard. *In re Woodruff,* 919 F.2d 1575, 1577, 16 U.S.P.Q.2d 1934, 1935 (Fed.Cir.1990).

[2] Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia,* consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir.1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id.*

[3] We agree with appellants that the PTO has not established the prima facie obviousness of the claimed subject matter. The prior art simply does not disclose or suggest the expression in cyanobacteria of a chimeric gene encoding an insecticidally active protein, or convey to those of ordinary skill a reasonable expectation of success in doing so. More particularly, there is no suggestion in Dzelzkalns, the primary reference cited against all claims, of substituting in the disclosed plasmid a structural gene encoding *Bacillus* insecticidal proteins for the CAT gene utilized for selection purposes. The expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria for unrelated purposes.

The PTO argues that the substitution of insecticidal *Bacillus* genes for CAT marker genes in cyanobacteria is suggested by the secondary references Sekar I, Sekar II, and Ganesan, which collectively disclose expression of genes encoding *Bacillus* insecticidal proteins in two species of host *Bacillus* bacteria (*B. megaterium* and *B. subtilis*) as well as in the bacterium *E. coli.* While these references disclose expression of *Bacillus* genes encoding insecticidal proteins in certain transformed *bacterial* hosts, nowhere do these references disclose or suggest expression of such genes in transformed *cyanobacterial* hosts.

To remedy this deficiency, the PTO emphasizes similarity between bacteria and cyanobacteria, namely, that these are both procaryotic organisms, and argues that this fact would suggest to those of ordinary skill the use of cyanobacteria as hosts for expression of the claimed chimeric genes. While it is true that bacteria and cyanobacteria are now both classified as procaryotes, that fact alone is not sufficient to motivate the art worker as the PTO contends.***494** As the PTO concedes, cyanobacteria and bacteria are not identical; they are classified as two separate divisions of the kingdom Procaryotae.[FN21] Moreover, it is only in recent years that the biology of cyanobacteria has been clarified, as evidenced by references in the prior art

to "blue-green algae." Such evidence of recent uncertainty regarding the biology of cyanobacteria tends to rebut, rather than support, the PTO's position that one would consider the cyanobacteria effectively interchangeable with bacteria as hosts for expression of the claimed gene.

> FN21. *Stedman's Medical Dictionary* 1139 (24th ed. 1982) (definition of "Procaryotae"). Procaryotic organisms are commonly classified according to the following taxonomic hierarchy: Kingdom; Division; Class; Order; Family; Genus; Species. 3 *Bergey's Manual of Systematic Bacteriology* 1601 (1989).

At oral argument the PTO referred to additional secondary references, not cited against any independent claim (i.e., Friedberg, Miller, and Nierzwicki-Bauer), which it contended disclose certain amino acid sequence homology between bacteria and cyanobacteria. The PTO argued that such homology is a further suggestion to one of ordinary skill to attempt the claimed invention. We disagree. As with the Dzelzkalns, Sekar I, Sekar II, and Ganesan references discussed above, none of these additional references disclose or suggest that cyanobacteria could serve as hosts for expression of genes encoding *Bacillus* insecticidal proteins. In fact, these additional references suggest as much about *differences* between cyanobacteria and bacteria as they do about similarities. For example, Nierzwicki-Bauer reports that a certain nucleotide sequence (i.e., the -10 consensus sequence) in a particular cyanobacterium resembles an *E. coli* promoter, but that another nearby nucleotide sequence (the -35 region) does not. While Miller speaks of certain promoters of the bacteriophage Lambda that are recognized by both cyanobacterial and *E. coli* RNA polymerases, it also discloses that these promoters exhibited differing strengths when exposed to the different polymerases. Differing sensitivities of the respective polymerases to an inhibitor are also disclosed, suggesting differences in the structures of the initiation complexes.

The PTO asks us to agree that the prior art would lead those of ordinary skill to conclude that cyanobacteria are attractive hosts for expression of any and all heterologous genes. Again, we can not. The relevant prior art does indicate that cyanobacteria are attractive hosts for expression of both native and heterologous *genes involved in photosynthesis* (not surprisingly, for the capability of undergoing oxygenic photosynthesis is what makes the cyanobacteria unique among procaryotes). However, these references do not suggest that cyanobacteria would be equally attractive hosts for expression of *unrelated* heterologous genes, such as the claimed genes encoding *Bacillus* insecticidal proteins.

In *O'Farrell*, this court affirmed an obviousness rejection of a claim to a method for producing a "predetermined protein in a stable form" in a transformed bacterial host. 853 F.2d at 895, 7 U.S.P.Q.2d at 1674. The cited references included a prior art publication (the Polisky reference) whose three authors included two of the three coinventor-appellants. The main difference between the prior art and the claim at issue was that in Polisky, the heterologous gene was a gene for ribosomal RNA, while the claimed invention substituted a gene coding for a predetermined protein. *Id.* at 901, 7 U.S.P.Q.2d at 1679. Although, as the appellants therein pointed out, the ribosomal RNA gene is not normally translated into protein, Polisky mentioned preliminary evidence that the transcript of the ribosomal RNA gene was translated into protein, and further predicted that if a gene coding for a protein were to be substituted, extensive translation might result. *Id.* We thus affirmed, explaining that

> the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the [claimed] method could be used to make proteins.
>
> ....
>
> ***495** ... Polisky contained detailed enabling

methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.

Id. at 901-02, 7 U.S.P.Q.2d at 1679-80.

In contrast with the situation in *O'Farrell*, the prior art in this case offers no suggestion, explicit or implicit, of the substitution that is the difference between the claimed invention and the prior art. Moreover, the "reasonable expectation of success" that was present in *O'Farrell* is not present here. Accordingly, we reverse the § 103 rejections.

B. Enablement

[4] The first paragraph of 35 U.S.C. § 112 requires, *inter alia*, that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without "undue experimentation." *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed.Cir.1988). That *some* experimentation may be required is not fatal; the issue is whether the amount of experimentation required is "undue." *Id.* at 736-37, 8 U.S.P.Q.2d at 1404. Enablement, like obviousness, is a question of law which we independently review, although based upon underlying factual findings which we review for clear error. *See id.* at 735, 8 U.S.P.Q.2d at 1402.

[5] In response to the § 112 rejection, appellants assert that their invention is "pioneering," and that this should entitle them to claims of broad scope. Narrower claims would provide no real protection, appellants argue, because the level of skill in this art is so high, art workers could easily avoid the claims. Given the disclosure in their specification, appellants contend that any skilled microbiologist could construct vectors and transform many different cyanobacteria, using a variety of promoters and *Bacillus* DNA, and could easily determine whether or not the active *Bacillus* protein was successfully expressed by the cyanobacteria.

The PTO made no finding on whether the claimed invention is indeed "pioneering," and we need not address the issue here. With the exception of claims 47 and 48, the claims rejected under § 112 are not limited to any particular genus or species of cyanobacteria. The PTO's position is that the cyanobacteria are a diverse and relatively poorly studied group of organisms, comprising some 150 different genera, and that heterologous gene expression in cyanobacteria is "unpredictable." Appellants have not effectively disputed these assertions. Moreover, we note that only one particular species of cyanobacteria is employed in the working examples of appellants' specification, and only nine genera of cyanobacteria are mentioned in the entire document.

Taking into account the relatively incomplete understanding of the biology of cyanobacteria as of appellants' filing date, as well as the limited disclosure by appellants of particular cyanobacterial genera operative in the claimed invention, we are not persuaded that the PTO erred in rejecting claims 1-46 and 50-51 under § 112, first paragraph. There is no reasonable correlation between the narrow disclosure in appellants' specification and the broad scope of protection sought in the claims encompassing gene expression in any and all cyanobacteria. *See In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (CCPA 1970) (the first paragraph of § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification).[FN22] Accordingly, ***496** we affirm the § 112 rejection as to those claims.

FN22. The enablement rejection in this case was not based upon a post-filing date state of the art, as in *In re Hogan*, 559 F.2d 595, 605-07, 194 U.S.P.Q. 527, 536-38 (CCPA 1977). *See also United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1251, 9 U.S.P.Q.2d 1461, 1464

(Fed.Cir.1989) (citing *Hogan*); *Hormone Research Found., Inc. v. Genentech, Inc.*, 904 F.2d 1558, 1568-69, 15 U.S.P.Q.2d 1039, 1047-48 (Fed.Cir.1990) (directing district court, on remand, to consider effect of *Hogan* and *United States Steel* on the enablement analysis of *Fisher*),*cert. dismissed*,499 U.S. 955, 111 S.Ct. 1434, 113 L.Ed.2d 485 (1991). We therefore do not consider the effect of *Hogan* and its progeny on *Fisher's* analysis of when an inventor should be allowed to "dominate the future patentable inventions of others." *Fisher*, 427 F.2d at 839, 166 U.S.P.Q. at 24.

[6] In so doing we do *not* imply that patent applicants in art areas currently denominated as "unpredictable" must never be allowed generic claims encompassing more than the particular species disclosed in their specification. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Angstadt*, 537 F.2d 498, 502-03, 190 U.S.P.Q. 214, 218 (CCPA 1976). However, there must be sufficient disclosure, either through illustrative examples or terminology,[FN23] to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility. Where, as here, a claimed genus represents a diverse and relatively poorly understood group of microorganisms, the required level of disclosure will be greater than, for example, the disclosure of an invention involving a "predictable" factor such as a mechanical or electrical element. *See Fisher*, 427 F.2d at 839, 166 U.S.P.Q. at 24. In this case, we agree with the PTO that appellants' limited disclosure does not enable one of ordinary skill to make and use the invention as now recited in claims 1-46 and 50-51 without undue experimentation.

FN23. The first paragraph of § 112 requires nothing more than *objective* enablement. *In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (CCPA 1971). How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is irrelevant. *Id.*

Remaining dependent claim 47 recites a cyanobacterium which expresses the chimeric gene of claim 1, wherein the cyanobacterium is selected from among the genera *Anacystis* and *Synechocystis*. Claim 48, which depends from claim 47, is limited to the cyanobacterium *Synechocystis* 6803. The PTO did not separately address these claims, nor indicate why they should be treated in the same manner as the claims encompassing all types of cyanobacteria. Although these claims are not limited to expression of genes encoding particular *Bacillus* proteins, we note what appears to be an extensive understanding in the prior art of the numerous *Bacillus* proteins having toxicity to various insects. The rejection of claims 47-48 under § 112 will not be sustained.

CONCLUSION

The rejection of claims 1-48 and 50-52 under 35 U.S.C. § 103 is *reversed*. The rejection of claims 1-46 and 50-51 under 35 U.S.C. § 112, first paragraph, is *affirmed* and the rejection of claims 47 and 48 thereunder is *reversed*.

AFFIRMED-IN-PART, REVERSED-IN-PART.

MAYER, Circuit Judge, dissenting.

An appeal is not a second opportunity to try a case or prosecute a patent application, and we should not allow parties to "undertake to retry the entire case on appeal." *Perini America, Inc. v. Paper Converting Machine Co.*, 832 F.2d 581, 584, 4 U.S.P.Q.2d 1621, 1624 (Fed.Cir.1987); *Eaton Corp. v. Appliance Valves Corp.*, 790 F.2d 874, 877, 229 U.S.P.Q. 668, 671 (Fed.Cir.1986). But that is precisely what the court has permitted here. The PTO

conducted a thorough examination of the prior art surrounding this patent application and concluded the claims would have been obvious. The board's decision based on the examiner's answer which comprehensively explains the rejection is persuasive and shows how the evidence supports the legal conclusion that the claims would have been obvious. Yet, the court ignores all this and conducts its own examination, if you will, as though the examiner and board did not exist. Even if I thought this opinion were more persuasive than the board's, I could ***497** not join it because it misperceives the role of the court.

The scope and content of the prior art, the similarity between the prior art and the claims, the level of ordinary skill in the art, and what the prior art teaches are all questions of fact. *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S.Ct. 684, 693-94, 15 L.Ed.2d 545, 148 U.S.P.Q. 459, 467 (1966); *Jurgens v. McKasy*, 927 F.2d 1552, 1560, 18 U.S.P.Q.2d 1031, 1037 (Fed.Cir.1991). And "[w]here there are two permissible views of the evidence, the factfinder's choice between them cannot be clearly erroneous." *Anderson v. City of Bessemer City*, 470 U.S. 564, 574, 105 S.Ct. 1504, 1511-12, 84 L.Ed.2d 518 (1985). The mere denomination of obviousness as a question of law does not give the court license to decide the factual matters afresh and ignore the requirement that they be respected unless clearly erroneous. *In re Woodruff*, 919 F.2d 1575, 1577, 16 U.S.P.Q.2d 1934, 1935 (Fed.Cir.1990); *In re Kulling*, 897 F.2d 1147, 1149, 14 U.S.P.Q.2d 1056, 1057 (Fed.Cir.1990). There may be more than one way to look at the prior art, but on this record we are bound by the PTO's interpretation of the evidence because it is not clearly erroneous and its conclusion is unassailable. I would affirm on that basis.

C.A.Fed.,1991.
In re Vaeck
947 F.2d 488, 20 U.S.P.Q.2d 1438

END OF DOCUMENT

Exhibit 7

United States Court of Appeals,
Federal Circuit.
AMGEN, INC., Plaintiff/Cross-Appellant,
v.
CHUGAI PHARMACEUTICAL CO., LTD., and Genetics Institute, Inc., Defendants-Appellants.
Nos. 90-1273, 90-1275.

March 5, 1991.
Suggestion for Rehearing In Banc Declined May 20, 1991.

Owner of patent for DNA sequences encoding Erythropoietin (EPO) brought suit against owner of patent for method for purification of EPO and EPO compositions, claiming patent infringement, and seeking declaration that defendant's patent was invalid or, in the alternative, that plaintiff did not infringe claims of the patent, and declaration that defendants' future activities in the production and sale of EPO would infringe plaintiff's patent. Defendants counterclaimed, alleging patent infringement and unfair composition, and seeking declaratory judgment that plaintiff's patent was invalid and not infringed. The United States District Court for the District of Massachusetts, William G. Young, J., ruled that some claims of plaintiff's patent were valid and infringed, that other claims were invalid, but if valid, were infringed, and that some claims of defendant's patent were valid and infringed, that some claims were not infringed and that other claims were invalid for indefiniteness. Both parties appealed. The Court of Appeals, Lourie, Circuit Judge, held that: (1) plaintiff's invention had priority; (2) claims for plaintiff's patent were not obvious; (3) plaintiff's patent satisfied best mode requirement; (4) generic DNA sequence claims of plaintiff's patent did not satisfy enablement requirement; (5) there was no inequitable conduct in prosecution of plaintiff's patent; (6) claims for defendant's patent were not adequately enabled; and (7) other claims for defendant's patent were indefinite.

Affirmed in part, reversed in part and vacated in part.

West Headnotes

[1] Patents 291 ⇐90(1)

291 Patents
291III Persons Entitled to Patents
291k90 Original Inventors and Priority Between Inventors
291k90(1) k. In General. Most Cited Cases
"Conception," in determining priority of invention, is the formation in the mind of the inventor of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice; conception requires both the idea of the invention's structure and possession of an operative method of making it. 35 U.S.C.A. § 102(g).

[2] Patents 291 ⇐90(1)

291 Patents
291III Persons Entitled to Patents
291k90 Original Inventors and Priority Between Inventors
291k90(1) k. In General. Most Cited Cases
The conception for purified and isolated DNA sequences encoding human erythropoietin (EPO) did not occur, for purposes of determining priority of invention, until gene had been isolated; before the gene was cloned, the amino acid sequence for EPO was uncertain, and in some positions the sequence envisioned was incorrect. 35 U.S.C.A. § 102(g).

[3] Patents 291 ⇐90(1)

291 Patents
291III Persons Entitled to Patents
291k90 Original Inventors and Priority Between Inventors
291k90(1) k. In General. Most Cited Cases

Conception of chemical compound, for purposes of priority of invention, requires that inventor be able to define it so as to distinguish from other materials, and to describe how to obtain it; conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it.

[4] Patents 291 ⇐90(5)

291 Patents
291III Persons Entitled to Patents
291k90 Original Inventors and Priority Between Inventors
291k90(5) k. Reduction of Invention to Practice in General. Most Cited Cases
When inventor is unable to envision detailed constitution of gene so as to distinguish it from other materials, as well as method for obtaining it, conception, for purposes of priority of invention, has not been achieved until reduction to practice has occurred, i.e., until after gene has been isolated. 35 U.S.C.A. § 102(g).

[5] Patents 291 ⇐17(3)

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k17 Nature and Degree of Skill Involved
291k17(3) k. Particular Devices or Processes. Most Cited Cases
Unique probing and screening method employed by inventor in isolating human erythropoietin (EPO) gene was not obvious. 35 U.S.C.A. § 103.

[6] Patents 291 ⇐99

291 Patents
291IV Applications and Proceedings Thereon
291k99 k. Description of Invention in Specification. Most Cited Cases
Absent inequitable conduct, best mode defense only affects those claims covering subject matter the practice of which has not been disclosed in compliance with best mode requirement. 35 U.S.C.A. § 112.

[7] Patents 291 ⇐99

291 Patents
291IV Applications and Proceedings Thereon
291k99 k. Description of Invention in Specification. Most Cited Cases
In determining whether patent application sets forth best mode contemplated by inventor of carrying out his invention, court inquires whether, at time inventor filed his patent application, he contemplated a best mode of practicing his invention, and if he did, whether his disclosure is adequate to enable one skilled in the art to practice the best mode, or, in other words, whether best mode had been concealed from the public. 35 U.S.C.A. § 112.

[8] Patents 291 ⇐99

291 Patents
291IV Applications and Proceedings Thereon
291k99 k. Description of Invention in Specification. Most Cited Cases

Patents 291 ⇐167(1)

291 Patents
291IX Construction and Operation of Letters Patent
291IX(B) Limitation of Claims
291k167 Specifications, Drawings, and Models
291k167(1) k. In General. Most Cited Cases
Applicant for patent for DNA sequence encoding erythropoietin (EPO), an organism created by insertion of genetic material into cell obtained from generally available sources, was not required to place cell samples in public depository, where best mode of preparing cells had been disclosed, and cells could be prepared by one skilled in the art from known materials using description in the specifica-

tion. 35 U.S.C.A. § 112.

[9] Patents 291 ⇐99

291 Patents
291IV Applications and Proceedings Thereon
291k99 k. Description of Invention in Specification. Most Cited Cases
When organism is created by insertion of genetic material into cell obtained from generally available sources, best mode requirement is satisfied by description of the best mode and adequate description of means of carrying out the invention, not a deposit of the cells; if the cells can be prepared without undue experimentation from known materials, based on the description in the patent specification, a deposit is not required. 35 U.S.C.A. § 112.

[10] Patents 291 ⇐113(6)

291 Patents
291IV Applications and Proceedings Thereon
291k113 Appeals from Decisions of Commissioner of Patents
291k113(6) k. Review on Appeal in General. Most Cited Cases
Whether written description of invention is sufficient to enable person skilled in the art to make and use the same is a question of law, which Court of Appeals reviews de novo. 35 U.S.C.A. § 112.

[11] Patents 291 ⇐99

291 Patents
291IV Applications and Proceedings Thereon
291k99 k. Description of Invention in Specification. Most Cited Cases
That some experimentation is necessary to make or use claimed invention does not constitute lack of enablement; amount of experimentation, however, must not be unduly excessive. 35 U.S.C.A. § 112.

[12] Patents 291 ⇐99

291 Patents
291IV Applications and Proceedings Thereon
291k99 k. Description of Invention in Specification. Most Cited Cases
Generic claim, covering all possible DNA sequences that would encode any polypeptide having amino acid sequence "sufficiently duplicative" of erythropoietin (EPO) to possess the property of increasing production of red blood cells failed to disclose how to make and use enough sequences to justify grant of claim sought; patent claimed every possible analog of a gene containing about 4,000 nucleotides, with disclosure of how to make EPO and a very few analogs. 35 U.S.C.A. § 112.

[13] Patents 291 ⇐99

291 Patents
291IV Applications and Proceedings Thereon
291k99 k. Description of Invention in Specification. Most Cited Cases
It is not necessary that patent applicant test all embodiments of his invention; what is necessary is that he provide disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims. 35 U.S.C.A. § 112.

[14] Patents 291 ⇐101(1)

291 Patents
291IV Applications and Proceedings Thereon
291k101 Claims
291k101(1) k. In General. Most Cited Cases
Patent applicant is entitled to claim his invention generically, when he describes it sufficiently to meet best mode and enablement requirements. 35 U.S.C.A. § 112.

[15] Patents 291 ⇐97

291 Patents
291IV Applications and Proceedings Thereon
291k97 k. Patent Office and Proceedings Therein in General. Most Cited Cases
Central elements of proof of inequitable conduct by patent applicant include intent to deceive and materiality; after finding threshold levels of material-

ity and intent, trial court must balance the two and determine, in its discretion, whether inequitable conduct has occurred.

[16] Patents 291 ⇐324.5

291 Patents
291XII Infringement
291XII(C) Suits in Equity
291k324 Appeal
291k324.5 k. Scope and Extent of Review in General. Most Cited Cases
Court of Appeals reviews ultimate conclusion of inequitable conduct by patent applicant under abuse of discretion standard, but underlying factual threshold findings are reviewed under clearly erroneous standard.

[17] Patents 291 ⇐97

291 Patents
291IV Applications and Proceedings Thereon
291k97 k. Patent Office and Proceedings Therein in General. Most Cited Cases
There was no inequitable conduct in prosecuting patent for DNA sequences encoding erythropoietin (EPO); that inventor did not recall whether he first used screened monkey cDNA library with full set of probes or subset of probes, and his answer that "it looks like" he used the subset, were not clear admissions that he used only a subset, and even if there had been an erroneous statement, it was not material, as inventor succeeded encoding the EPO gene first with his use of fully-degenerate probes.

[18] Patents 291 ⇐101(5)

291 Patents
291IV Applications and Proceedings Thereon
291k101 Claims
291k101(5) k. Requisites and Sufficiency. Most Cited Cases
Claims for patent for method for purification of the erythropoietin (EPO) and EPO compositions, requiring 160,000 IU/AU by *in vivo* measurement, were not adequately enabled; *in vivo* data did not support claims containing an *in vivo* limitation. 35 U.S.C.A. § 112.

[19] Patents 291 ⇐101(5)

291 Patents
291IV Applications and Proceedings Thereon
291k101 Claims
291k101(5) k. Requisites and Sufficiency. Most Cited Cases
Whether patent claim satisfies requirement that "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention" requires determination whether those skilled in the art would understand what is claimed. 35 U.S.C.A. § 112.

[20] Patents 291 ⇐101(6)

291 Patents
291IV Applications and Proceedings Thereon
291k101 Claims
291k101(6) k. Ambiguity, Uncertainty or Indefiniteness. Most Cited Cases
Claims of patent for method of purification of erythropoietin (EPO) and EPO compositions were invalid because their specific activity limitation of "at least about 160,000" was indefinite. 35 U.S.C.A. § 112.

[21] Patents 291 ⇐101(6)

291 Patents
291IV Applications and Proceedings Thereon
291k101 Claims
291k101(6) k. Ambiguity, Uncertainty or Indefiniteness. Most Cited Cases
When meaning of patent claims is in doubt, especially when there is close prior art, they are properly declared invalid. 35 U.S.C.A. § 112.

[22] Patents 291 ⇐97

291 Patents
291IV Applications and Proceedings Thereon
291k97 k. Patent Office and Proceedings

Therein in General. Most Cited Cases
To establish inequitable conduct with respect to patent, intent to deceive is required.

[23] Patents 291 ⇐97

291 Patents
291IV Applications and Proceedings Thereon
291k97 k. Patent Office and Proceedings Therein in General. Most Cited Cases
Finding of intent to deceive, required to establish inequitable conduct with respect to patent, may follow from assessment of materiality, knowledge, and surrounding circumstances, including evidence of good faith.

[24] Patents 291 ⇐97

291 Patents
291IV Applications and Proceedings Thereon
291k97 k. Patent Office and Proceedings Therein in General. Most Cited Cases
There was no inequitable conduct with respect to patent for method for purification of erythropoietin (EPO) and EPO compositions, despite contention that patent owner displayed intent to mislead by withholding data showing *in vivo* specific activity of homogeneous EPO and withholding information on range of error in EPO bioassays.

Patents 291 ⇐328(2)

291 Patents
291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents
291k328 Patents Enumerated
291k328(2) k. Original Utility. Most Cited Cases
4,677,195. Claims 1, 3, 4, 6 invalid.

Patents 291 ⇐328(2)

291 Patents
291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents
291k328 Patents Enumerated
291k328(2) k. Original Utility. Most Cited Cases
4,703,008. Claims 2, 4, 6, valid and infringed claims 7, 8, 23-27, 29 invalid.

***1202** Edward M. O'Toole,Marshall, O'Toole, Gerstein, Murray & Bicknall, Chicago, Ill., argued, for plaintiff/cross-appellant. With him on the brief were Michael F. Borun, Richard A. Schnurr and Christine A. Dudzik. Also on the brief were Steven M. Odre and Robert D. Weist, Amgen, Inc., Thousand Oaks, Cal., of counsel.

Kurt E. Richter, Morgan & Finnegan, New York City, and William F. Lee, Hale & Dorr, Boston, Mass., argued for defendants-appellants. Of counsel were Eugene Moroz, Michael P. Dougherty and William S. Feiler, Morgan & Finnegan, New York City.

Before MARKEY, LOURIE and CLEVENGER, Circuit Judges.

LOURIE, Circuit Judge.

This appeal and cross appeal are from the March 4, 1990, judgment of the United States District Court for the District of Massachusetts, *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 13 USPQ2d 1737, 1989 WL 169006 (1990), and involve issues of patent validity, infringement, and inequitable conduct with respect to two patents: U.S. Patent 4,703,008 ('008), owned by Kirin-Amgen Inc. (Amgen), and U.S. Patent 4,677,195 ('195), owned by Genetics Institute, Inc. (GI).

***1203** Chugai Pharmaceutical Co., Ltd. (Chugai) and Genetics Institute, Inc. (collectively defendants) assert on appeal that the district court erred in holding that: 1) Amgen's '008 patent is not invalid under 35 U.S.C. §§ 102(g) and 103; 2) the '008 patent is enforceable; 3) the failure of Amgen to deposit the best mode host cells was not a violation of the best mode requirement under 35 U.S.C. § 112; and 4) claims 4 and 6 of GI's '195 patent are invalid for indefiniteness under 35 U.S.C. § 112.

On cross appeal, Amgen challenges the district court's holdings that: 1) claims 1 and 3 of the '195 patent are enabled; 2) the '195 patent is enforceable; 3) this is not an exceptional case warranting an award of attorney fees to Amgen; and 4) claims 7, 8, 23-27 and 29 of the '008 patent are not enabled by the specification.

We affirm the district court's holdings in all respects, except that we reverse the court's ruling that claims 1 and 3 of the '195 patent are enabled. We also vacate that part of the district court's judgment relating to infringement of those claims.

BACKGROUND [FN1]

FN1. The district court, in a detailed opinion, fully sets out the scientific and historical background relating to the patents at issue. *See Amgen,* 13 USPQ2d at 1741-58. Familiarity with that opinion is presumed.

Erythropoietin (EPO) is a protein consisting of 165 amino acids which stimulates the production of red blood cells. It is therefore a useful therapeutic agent in the treatment of anemias or blood disorders characterized by low or defective bone marrow production of red blood cells.

The preparation of EPO products generally has been accomplished through the concentration and purification of urine from both healthy individuals and those exhibiting high EPO levels. A new technique for producing EPO is recombinant DNA technology in which EPO is produced from cell cultures into which genetically-engineered vectors containing the EPO gene have been introduced. The production of EPO by recombinant technology involves expressing an EPO gene through the same processes that occur in a natural cell.

THE PATENTS

On June 30, 1987, the United States Patent and Trademark Office (PTO) issued to Dr. Rodney Hewick U.S. Patent 4,677,195, entitled "Method for the Purification of Erythropoietin and Erythropoietin Compositions"(the '195 patent). The patent claims both homogeneous EPO and compositions thereof and a method for purifying human EPO using reverse phase high performance liquid chromatography. The method claims are not before us. The relevant claims of the '195 patent are:

1. Homogeneous erythropoietin characterized by a molecular weight of about 34,000 daltons on SDS PAGE, movement as a single peak on reverse phase high performance liquid chromatography and a specific activity of at least 160,000 IU per absorbance unit at 280 nanometers.

* * * * * *

3. A pharmaceutical composition for the treatment of anemia comprising a therapeutically effective amount of the homogeneous erythropoietin of claim 1 in a pharmaceutically acceptable vehicle.

4. Homogeneous erythropoietin characterized by a molecular weight of about 34,000 daltons on SDS PAGE, movement as a single peak on reverse phase high performance liquid chromatography and a specific activity of at least about 160,000 IU per absorbance unit at 280 nanometers.

* * * * * *

6. A pharmaceutical composition for the treatment of anemia comprising a therapeutically effective amount of the homogeneous erythropoietin of claim 4 in a pharmaceutically acceptable vehicle.

Dr. Hewick assigned the patent to GI.

The other patent in this litigation is U.S. Patent 4,703,008, entitled "DNA Sequences Encoding Erythropoietin" (the '008 patent), issued on October 27, 1987, to Dr. Fu-Kuen Lin, an employee of Amgen. The claims of ***1204** the '008 patent cover purified and isolated DNA sequences encoding erythropoietin and host cells transformed or transfected

with a DNA sequence. The relevant claims are as follows:

2. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.

* * * * * *

4. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 1, 2 or 3 in a manner allowing the host cell to express erythropoietin.

* * * * * *

6. A procaryotic or eucaryotic host cell stably transformed or transfected with a DNA vector according to claim 5.

7. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.

8. A cDNA sequence according to claim 7.

* * * * * *

23. A procaryotic or eucaryotic host cell transformed or transfected with a DNA sequence according to claim 7, 8, or 11 in a manner allowing the host cell to express said polypeptide.

24. A transformed or transfected host cell according to claim 23 which host cell is capable of glycosylating said polypeptide.

25. A transformed or transfected mammalian host cell according to claim 24.

26. A transformed or transfected COS cell according to claim 25.

27. A transformed or transfected CHO cell according to claim 25.

* * * * * *

29. A procaryotic host cell stably transformed or transfected with a DNA vector according to claim 28.

PROCEDURAL HISTORY

On October 27, 1987, the same day that the '008 patent was issued, Amgen filed suit against Chugai and GI. It alleged that GI infringed the '008 patent by the production of recombinant EPO (rEPO) and by use of transformed mammalian host cells containing vectors with DNA coding for the production of human EPO, and that Chugai, as a result of a collaborative relationship with GI, had induced and/or contributed to the direct infringement of the '008 patent by GI. Amgen further sought a declaration that GI's '195 patent is invalid under 35 U.S.C. §§ 102, 103, and 112, or, in the alternative, that Amgen does not infringe the claims of the '195 patent, and a declaration that GI and Chugai's future activities in the production and sale of rEPO will infringe the '008 patent.[FN2]

FN2. Amgen subsequently filed a complaint with the United States International Trade Commission alleging that Chugai's importation of rEPO, manufactured in Japan using genetically engineered host cells, violated Section 337 of the Tariff Act of 1930 (19 U.S.C. § 1337, 1337a). The Commission entered an order terminating the investigation for lack of subject matter jurisdiction. This court vacated and remanded, holding that the Commission should have treated the complaint on the merits and not on jurisdictional grounds, and that the claims of Amgen's patent did not cover a process for producing rEPO. *Amgen, Inc. v. United States Int'l Trade Comm'n,* 902 F.2d 1532, 14 USPQ2d 1734

(Fed.Cir.1990).

GI and Chugai answered and counterclaimed, asserting several affirmative defenses, including invalidity under 35 U.S.C. §§ 101, 102, 103, and 112; non-infringement; failure to make deposits at a public depository of biological materials allegedly necessary for enabling the best mode of practicing the invention; and unenforceability of the patent because of Amgen's alleged inequitable conduct before the PTO. GI also counterclaimed, alleging that Amgen infringed the '195 patent, asserting unfair competition, and seeking a declaratory judgment that the '008 patent was invalid and not infringed.

GI and Chugai then filed a joint motion for a partial summary judgment that Amgen***1205** infringed the claims of the '195 patent. Chugai also filed its own motion for summary judgment. On February 24, 1988, the district court granted GI's and Chugai's motion for partial summary judgment and, on January 31, 1989, the court granted Chugai's motion for partial summary judgment only to the extent of ruling that the '008 patent does not contain a process claim, an issue that is not now before us.

In response to Amgen's motion for a preliminary injunction, the district court, on February 7, 1989, issued an order finding that "Amgen had shown a reasonable likelihood of success on the merits of the validity of its patent; that it would suffer irreparable injury due to the needs of an incipient market and the attendant burdens on a new company; ..." and that, as to the public interest, "recombinant EPO is an extraordinarily valuable medicine that promises marked relief from renal failure." Because of this public interest finding, the court determined that it would not enter an order to delay or prevent production or shipping of EPO, but would require the defendant GI to place with the court all profits from the sale of EPO.

In order to expedite trial, the parties consented to trial before a magistrate. The judge entered judgment upon findings of fact and conclusions of law set forth by the magistrate. With respect to Amgen's '008 patent, the court held that claims 2, 4, and 6 are valid, enforceable and have been infringed by GI; that infringement was not willful; that claims 7, 8, 23-27, and 29 are invalid for lack of enablement under 35 U.S.C. § 112 but, if valid, were infringed by GI; that the '008 patent does not contain a process claim; and that Chugai has not infringed, contributorily infringed, or induced infringement of any claim of the '008 patent. The court also dismissed Amgen's complaint against Chugai.

With respect to GI's '195 patent, the court concluded that claims 1 and 3 are valid, enforceable, and have been infringed by Amgen; that Amgen has not infringed claims 2 and 5; that Amgen's infringement was not willful; and that claims 4 and 6 are invalid for indefiniteness under 35 U.S.C. § 112, but, if valid, were infringed by Amgen. The court also concluded that Amgen did not misuse the '008 patent and that this was not an "exceptional" case under 35 U.S.C. § 285.

DISCUSSION

I. AMGEN's '008 PATENT (Lin)

A. *Alleged prior invention under 35 U.S.C. § 102(g)*

The first issue we review is whether the district court erred in finding that the claims directed to a purified and isolated DNA sequence encoding human EPO were not invalidated by the work of GI's Dr. Fritsch. Section 102(g) provides in relevant part that:

A person is entitled to a patent unless-

(g) before the applicant's invention thereof the invention was made ... by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention,

but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

Defendants assert error in the district court's legal conclusion that in this case Lin's conception occurred simultaneously with reduction to practice. *See e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1376, 231 USPQ 81, 87 (Fed.Cir.1986), *cert. denied*,480 U.S. 947, 107 S.Ct. 1606, 94 L.Ed.2d 792 (1987). They claim that Fritsch was first to conceive a probing strategy of using two sets of fully-degenerate cDNA probes of two different regions of the EPO gene to screen a gDNA library, which was the strategy which the district court found eventually resulted in the successful identification and isolation of the EPO gene. Defendants further claim that Fritsch conceived this strategy in 1981, was diligent until he reduced the invention to practice in May of 1984, and thus should be held to be a § 102(g) prior ***1206** inventor over Lin, who reduced the invention to practice in September of 1983.

[1] Conception is the "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." *Hybritech*, 802 F.2d at 1376, 231 USPQ at 87 (citing 1 *Robinson on Patents* 532 (1890)); *Coleman v. Dines*, 754 F.2d 353, 359, 224 USPQ 857, 862 (Fed.Cir.1985) (citing *Gunter v. Stream*, 573 F.2d 77, 80, 197 USPQ 482, 484 (CCPA 1978)). Conception requires both the idea of the invention's structure and possession of an operative method of making it. *Oka v. Youssefyeh*, 849 F.2d 581, 583, 7 USPQ2d 1169, 1171 (Fed.Cir.1988).

[2] In some instances, an inventor is unable to establish a conception until he has reduced the invention to practice through a successful experiment. This situation results in a simultaneous conception and reduction to practice. *See* 3 D. Chisum, *Patents* § 10.04[5] (1990). We agree with the district court that that is what occurred in this case.

The invention recited in claim 2 is a "purified and isolated DNA sequence" encoding human EPO. The structure of this DNA sequence was unknown until 1983, when the gene was cloned by Lin; Fritsch was unaware of it until 1984. As Dr. Sadler, an expert for GI, testified in his deposition: "You have to clone it first to get the sequence." In order to design a set of degenerate probes, one of which will hybridize with a particular gene, the amino acid sequence, or a portion thereof, of the protein of interest must be known. Prior to 1983, the amino acid sequence for EPO was uncertain, and in some positions the sequence envisioned was incorrect. Thus, until Fritsch had a complete mental conception of a purified and isolated DNA sequence encoding EPO and a method for its preparation, in which the precise identity of the sequence is envisioned, or in terms of other characteristics sufficient to distinguish it from other genes, all he had was an objective to make an invention which he could not then adequately describe or define.

[3][4] A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. *See Oka*, 849 F.2d at 583, 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated.

Fritsch had a goal of obtaining the isolated EPO gene, whatever its identity, and even had an idea of a possible method of obtaining it, but he did not conceive a purified and isolated DNA sequence encoding EPO and a viable method for obtaining it until after Lin. It is important to recognize that neither Fritsch nor Lin invented EPO or the EPO gene. The subject matter of claim 2 was the novel *purified and isolated* sequence which codes for EPO, and neither Fritsch nor Lin knew the structure or physical characteristics of it and had a viable method of obtaining that subject matter until it was actually obtained and characterized.

Defendants further argue that because the trial court found that the probing and screening method employed by Lin is what distinguished the invention of the '008 patent over the prior art, Fritsch's strategy in 1981 had priority over Lin's use of that strategy. We disagree. The trial court found that Fritsch's alleged conception in 1981 of an approach that might result in cloning the gene was mere speculation. ***1207** Conception of a generalized approach for screening a DNA library that might be used to identify and clone the EPO gene of then unknown constitution is not conception of a "purified and isolated DNA sequence" encoding human EPO. It is not "a definite and permanent idea of the complete and operative invention." Fritsch's conception of a process had to be sufficiently specific that one skilled in the relevant art would succeed in cloning the EPO gene. *See Coleman,* 754 F.2d at 359, 224 USPQ at 862. Clearly, he did not have that conception because he did not know the structure of EPO or the EPO gene.

The record indicates that several companies, as well as Amgen and GI, were unsuccessful using Fritsch's approach. As the trial court correctly summarized:

> Given the utter lack of experience in probing genomic libraries with fully degenerate probes and the crudeness of the techniques available in 1981, it would have been mere speculation or at most a probable deduction from facts then known by Dr. Fritsch that his generalized approach would result in cloning the EPO gene.

13 USPQ2d at 1760. As expert testimony from both sides indicated, success in cloning the EPO gene was not assured until the gene was in fact isolated and its sequence known. Based on the uncertainties of the method and lack of information concerning the amino acid sequence of the EPO protein, the trial court was correct in concluding that neither party had an adequate conception of the DNA sequence until reduction to practice had been achieved; Lin was first to accomplish that goal.

Defendants also argue that the court failed to consider that 1983, just prior to Lin's conception, was the relevant time for determining the completeness of Fritsch's conception, not 1981. However, the record shows that the court did consider what occurred in 1983. Moreover, Fritsch had no more of a conception in 1983 than he did in 1981, because he did not then know the sequence of the gene encoding EPO.

B. *Alleged obviousness of the inventions of claims 2, 4, and 6*

Claim 2, as noted above, recites a purified and isolated DNA sequence, and claims 4 and 6 are directed to host cells transformed with such a DNA sequence. The district court determined that claims 2, 4, and 6 are not invalid under 35 U.S.C. § 103, concluding that the unique probing and screening method employed by Lin in isolating the EPO gene and the extensive effort required to employ that method made the invention nonobvious over the prior art.[FN3]

> FN3. We note that both the district court and the parties have focused on the obviousness of a process for making the EPO gene, despite the fact that it is products (genes and host cells) that are claimed in the patent, not processes. We have directed our attention accordingly, and do not consider independently whether the products

would have been obvious aside from the alleged obviousness of a method of making them.

Obviousness under Section 103 is a question of law. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568, 1 USPQ2d 1593, 1597 (Fed.Cir.), *cert. denied*,481 U.S. 1052, 107 S.Ct. 2187, 95 L.Ed.2d 843 (1987). The district court stated that one must inquire whether the prior art would have suggested to one of ordinary skill in the art that Lin's probing and screening method should be carried out and would have a reasonable expectation of success, viewed in light of the prior art. *See In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed.Cir.1988). "Both the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure." *Id.*

The district court specifically found that, as of 1983, none of the prior art references "suggest[s] that the probing strategy of using two fully-redundant [sic] sets of probes, of relatively high degeneracy [sic], to screen a human genomic library would be likely to succeed in pulling out the gene of interest." [FN4] 13 USPQ2d at 1768. While ***1208** it found that defendants had shown that these procedures were "obvious to try," the references did not show that there was a reasonable expectation of success. *See In re O'Farrell*, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1680-81 (Fed.Cir.1988).

FN4. At this point, some explanation of the involved technology may be useful, consistent with that expressed in the district court opinion. DNA consists of two complementary strands of nucleotides, which include the four basic compounds adenine(A), guanine(G), cytosine(C), and thymine(T), oriented so that bases from one strand weakly bond to the bases of the opposite strand. A bonds with T, and G bonds with C to form complementary base pairs. This bonding process is called hybridization and results in the formation of a stable duplex molecule. The structure also includes 5-carbon sugar moieties with phosphate groups.

The genetic code for a particular protein depends upon sequential groupings of three nucleotides, called codons. Each codon codes for a particular amino acid. Since there are four nucleotide bases and three bases per codon, there are 64 (4x4x4) possible codons. Because there are only 20 natural amino acids, most amino acids are specified by more than one codon. This is referred to as a "redundancy" or "degeneracy" in the genetic code, a fact that complicates and renders more difficult the techniques of recombinant DNA.

In order to prepare a protein using recombinant DNA technology, the gene for the protein must first be isolated from a cell's total DNA by screening a library of that cell's DNA. The DNA library is screened by use of a probe, a synthetic radiolabelled nucleic acid sequence which can be used to detect and isolate complementary base sequences by hybridization. To design a probe when the gene has not yet been isolated, a scientist must know the amino acid sequence, or a portion thereof, of the protein of interest. Because some amino acids have several possible codons and the researcher cannot know which of the possible codons will actually code for an amino acid, he or she may decide to design a set of probes that covers all possible codons for each amino acid comprising the protein, known as a "fully-degenerate" set of probes. A library to be screened can be a genomic library (gDNA), which contains a set of all the DNA sequences found in an organism's cells or a complementary DNA (cDNA) library, which is much smaller

> and less complex than a gDNA library, and is used frequently when the tissue source for a given gene is known.

[5] Defendants challenge the district court's determination, arguing that, as of September 1983, one of ordinary skill in the art would have had a reasonable expectation of success in screening a gDNA library by Lin's method in order to obtain EPO. We agree with the district court's conclusion, which was supported by convincing testimony. One witness, Dr. Davies of Biogen, another biotechnology company that had worked on EPO, stated that he could not say whether Biogen scientists would have succeeded in isolating the EPO gene if Biogen had the EPO fragments that were available to Lin in 1983. Dr. Wall, a professor at UCLA, testified that it would have been "difficult" to find the gene in 1983, and that there would have been no more than a fifty percent chance of success. He said, "you couldn't be certain where in the genomic DNA your probe might fall." The court found that no one had successfully screened a genomic library using fully-degenerate probes of such high redundancy as the probes used by Lin. In the face of this and other evidence on both sides of the issue, it concluded that defendants had not shown by clear and convincing evidence that the procedures used by Lin would have been obvious in September 1983. We are not persuaded that the court erred in its decision.

Defendants assert that whether or not it would have been obvious to isolate the human EPO gene from a gDNA library with fully-degenerate probes is immaterial because it was obvious to use the already known monkey EPO gene as a probe. Defendants point out that, in the early 1980s, Biogen did significant work with an EPO cDNA obtained from a baboon, and that they used it as a probe to hybridize with the corresponding gene in a human gDNA library. However, this technique did not succeed until after Lin isolated the EPO gene with his fully-degenerate set of probes.

To support its obviousness assertion, defendants rely upon the testimony of their expert, Dr. Flavell, who testified that the overall homology of baboon DNA and human DNA was "roughly 90 percent". While this testimony indicates that it might have been feasible, perhaps obvious to try, to successfully probe a human gDNA library with a monkey cDNA probe, it does not indicate that the gene could have been identified and isolated with a reasonable likelihood of success. Neither the DNA nucleotide sequence of the human EPO gene nor its exact degree of homology with ***1209** the monkey EPO gene was known at the time.

Indeed, the district court found that Lin was unsuccessful at probing a human gDNA library with monkey cDNA until after he had isolated the EPO gene by using the fully-degenerate probes. Based on the evidence in the record, the district court found there was no reasonable expectation of success in obtaining the EPO gene by the method that Lin eventually used. While the idea of using the monkey gene to probe for a homologous human gene may have been obvious to try, the realization of that idea would not have been obvious. There were many pitfalls. Hindsight is not a justifiable basis on which to find that ultimate achievement of a long sought and difficult scientific goal was obvious. The district court thoroughly examined the evidence and the testimony. We see no error in its result. Moreover, if the DNA sequence was not obvious, host cells containing such sequence, as claimed in claims 4 and 6, could not have been obvious. We conclude that the district court did not err in holding that the claims of the patent are not invalid under Section 103.

C. *Best Mode*

Defendants argue that the district court erred in failing to hold the '008 patent invalid under 35 U.S.C. § 112, asserting that Lin failed to disclose the best mammalian host cells known to him as of November 30, 1984, the date he filed his fourth patent application.

[6] The district court found that the "best mode" of practicing the claimed invention was by use of a specific genetically-heterogeneous strain of Chinese hamster ovary (CHO) cells, which produced EPO at a rate greater than that of other cells. It further found that this strain was disclosed in Example 10 and that Lin knew of no better mode. GI argues that Lin's best mode was not adequately disclosed in Example 10 because one skilled in the art could not duplicate Lin's best mode without his having first deposited a sample of the specific cells in a public depository. The issue before us therefore is whether the district court erred in concluding that Example 10 of the '008 patent satisfied the best mode requirement as to the invention of the challenged claims [FN5] and that a deposit of the preferred CHO cells was not necessary.

> FN5. Defendants assert that all the claims should be invalid for failure to disclose the best mode. We perceive that the best mode issue only relates to the host cell claims, 4, 6, 23-27, and 29. Absent inequitable conduct, a best mode defense only affects those claims covering subject matter the practice of which has not been disclosed in compliance with the best mode requirement. *See Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 940, 15 USPQ2d 1321, 1328 (Fed.Cir.), *cert. denied*,498 U.S. 920, 111 S.Ct. 296, 112 L.Ed.2d 250 (1990).

A determination whether the best mode requirement is satisfied is a question of fact, *DeGeorge v. Bernier*, 768 F.2d 1318, 1324, 226 USPQ 758, 763 (Fed.Cir.1985); we therefore review the district court's finding under a clearly erroneous standard.

35 U.S.C. § 112 provides in relevant part:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, *and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

(Emphasis added).

[7][8] This court has recently discussed the best mode requirement, pointing out that its analysis has two components. *Chemcast Corp. v. Arco Indus. Corp.*, 913 F.2d 923, 927, 16 USPQ2d 1033, 1036 (Fed.Cir.1990). The first is a subjective one, asking whether, at the time the inventor filed his patent application, he contemplated a best mode of practicing his invention. If he did, the second inquiry is whether his disclosure is adequate to enable one skilled in the art to practice the best mode or, in other words, whether the best mode has been concealed from the public. The best mode requirement thus is intended to ensure that a patent applicant ***1210** plays "fair and square" with the patent system. It is a requirement that the *quid pro quo* of the patent grant be satisfied. One must not receive the right to exclude others unless at the time of filing he has provided an adequate disclosure of the best mode known to him of carrying out his invention. Our case law has interpreted the best mode requirement to mean that there must be no concealment of a mode known by the inventor to be better than that which is disclosed. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384-85, 231 USPQ 81, 94 (Fed.Cir.1986), *cert. denied*,480 U.S. 947, 107 S.Ct. 1606, 94 L.Ed.2d 792 (1987). Section 282 imposes on those attempting to prove invalidity the burden of proof. We agree that the district court did not err in finding that defendants have not met their burden of proving a best mode violation.

As noted above, the district court found that the best mode of making the CHO cells was set forth in Example 10. As the district court stated, while it was not clear which of two possible strains Lin considered to be the best, the cell strain subjected to 1000 nanomolar MTX (methotrexate) or that subjected to 100 nanomolar MTX, the best mode was

disclosed because both were disclosed.[FN6] Defendants argue that this disclosure is not enough, that a deposit of the cells was required.

> FN6. In its opinion, the district court stated that "the best way to express EPO was from mammalian cells ... and that a cell line derived from 11 possible clones from the CHO B11 3,.1 cell strain was to be used for Amgen's master working cell bank, which was expected to be started on November 26, 1984." 13 USPQ2d at 1772. At another point, the court stated that Amgen "did disclose the best mode in Example 10 of the invention, when it described the production rates of the 100 nanomolar-amplified cells (the B11 3,.1 cell strain) and one micromolar-treated cells." *Id.*

Defendants contend that "[i]n the field of living materials such as microorganisms and cell cultures," we should require a biological deposit so that the public has access to exactly the best mode contemplated by the inventor. This presents us with a question of first impression concerning the best mode requirement for patents involving novel genetically-engineered biological subject matter.

For many years, it has been customary for patent applicants to place microorganism samples in a public depository when such a sample is necessary to carry out a claimed invention. This practice arose out of the development of antibiotics, when microorganisms obtained from soil samples uniquely synthesized antibiotics which could not be readily prepared chemically or otherwise. *In re Argoudelis,* 434 F.2d 1390, 168 USPQ 99 (CCPA 1970). Such a deposit has been considered adequate to satisfy the *enablement* requirement of 35 U.S.C. § 112, when a written description alone would not place the invention in the hands of the public and physical possession of a unique biological material is required. *See, e.g., In re Wands,* 858 F.2d 731, 735-36, 8 USPQ2d 1400, 1403 (Fed.Cir.1988) ("Where an invention depends on the use of living materials ... it may be impossible to enable the public to make the invention (*i.e.,* to obtain these living materials) solely by means of written disclosure."); *In re Lundak,* 773 F.2d 1216, 1220, 227 USPQ 90, 93 (Fed.Cir.1985) ("When an invention relates to a new biological material, the material may not be reproducible even when detailed procedures and a complete taxonomic description are included in the specification."); *see generally* Hampar, *Patenting of Recombinant DNA Technology: The Deposit Requirement,* 67 J. Pat. & Trademark Off. Soc'y 569, 607 (1985) ("The deposit requirement is a nonstatutory mechanism for ensuring compliance with the 'enabling' provision under 35 U.S.C. § 112.").

The district court found that the claims at issue require the use of biological materials that were capable of being prepared in the laboratory from readily available biological cells, using the description in Example 10. The court also found that there were no starting materials that were not publicly available, that were not described, or that required undue experimentation for their preparation in order to carry out the best mode. The court noted that Lin testified***1211** that the isolation of the preferred strain was a "routine limited dilution cloning procedure[ ]" well known in the art. Dr. Simonsen, GI's own expert, testified that the disclosed procedures were "standard" and that:

> with the vectors and the sequences shown in Example 10, I have no doubt that someone eventually could reproduce-well, could generate cell lines [sic, strains] making some level of EPO, and they could be better, they could be worse in terms of EPO production.

The district court relied on this testimony, and, upon review, we agree with its determination. The testimony accurately reflects that the invention, as it relates to the *best mode* host cells, could be practiced by one skilled in the art following Example 10. Thus, the best mode was disclosed and it was adequately enabled.

[9] These materials are therefore not analogous to

the biological cells obtained from unique soil samples. When a biological sample required for the practice of an invention is obtained from nature, the invention may be incapable of being practiced without access to that organism. Hence the deposit is required in that case. On the other hand, when, as is the case here, the organism is created by insertion of genetic material into a cell obtained from generally available sources, then all that is required is a description of the best mode and an adequate description of the means of carrying out the invention, not deposit of the cells. If the cells can be prepared without undue experimentation from known materials, based on the description in the patent specification, a deposit is not required. *See Feldman v. Aunstrup,* 517 F.2d 1351, 1354, 186 USPQ 108, 111 (CCPA 1975), ("No problem exists when the microorganisms used are known and readily available to the public."), *cert. denied,*424 U.S. 912, 96 S.Ct. 1109, 47 L.Ed.2d 316 (1976). Since the court found that that is the case here, we therefore hold that there is no failure to comply with the best mode requirement for lack of a deposit of the CHO cells, when the *best mode* of preparing the cells has been disclosed and the best mode cells have been enabled, *i.e.,* they can be prepared by one skilled in the art from known materials using the description in the specification.

Defendants also contend that the examiner's rejection of the application that matured into the '008 patent for failure to make a publicly accessible biological deposit supports its argument. U.S. Patent Application Serial No. 675,298, Prosecution History at 179 (First Rejection July 3, 1986). However, that rejection was withdrawn after an oral interview and a written argument that the invention did not require a deposit. *Id.* at 208.

We also note that the PTO has recently prescribed guidelines concerning the deposit of biological materials. *See*37 C.F.R. § 1.802(b) (1990) (biological material need not be deposited "if it is known and readily available to the public or can be made or isolated without undue experimentation"). The PTO, in response to a question as to whether the deposit requirement is applicable to the best mode requirement, as distinct from enablement, said:

> The best mode requirement is a safeguard against the possible selfish desire on the part of some people to obtain patent protection without making a full disclosure. The requirement does not permit an inventor to disclose only what is known to be the second-best embodiment, retaining the best.... The fundamental issue that should be addressed is whether there was evidence to show that the quality of an applicant's best mode disclosure is so poor as to effectively result in concealment. *In re Sherwood,* 615 [613] F.2d 809, 204 USPQ 537 (CCPA 1980). If a deposit is the only way to comply with the best mode requirement then the deposit must be made.

52 *Fed.Reg.* 34080, 34086 (Sept. 8, 1987).[FN7]

FN7. *See also*53 *Fed.Reg.* 39420, 39425 (Oct. 6, 1989) (comment *re*"deposit [to] satisfy the best mode requirement"); 52 *Fed.Reg.* 34080, 34080 and 34084 (Sept. 8, 1987) (deposit may be required to satisfy enablement, best mode, or distinct claim requirements of § 112).

We see no inconsistency between the district court's decision, which we affirm here, and these guidelines.

***1212** Defendants also assert that the record shows that scientists were unable to duplicate Lin's genetically-heterogeneous best mode cell strain. However, we have long held that the issue is whether the disclosure is "adequate," not that an exact duplication is necessary. Indeed, the district court stated that

> [t]he testimony is clear that no scientist could ever duplicate exactly the best mode used by Amgen, but that those of ordinary skill in the art could produce mammalian host cell strains or lines with similar levels of production identified in Example

10.

13 USPQ2d at 1774. What is required is an adequate disclosure of the best mode, not a guarantee that every aspect of the specification be precisely and universally reproducible. *See In re Gay,* 309 F.2d 769, 773, 135 USPQ 311, 316, 50 CCPA 725 (1962).

Defendants finally argue that Lin's failure to deposit the transfected cells notwithstanding the fact that he was willing to deposit essentially worthless cell material was evidence of deliberate concealment. We have already stated that deposit of the host cells containing the rEPO gene was not necessary to satisfy the best mode requirement of Section 112. The best mode was disclosed and a deposit was not necessary to carry it out. Therefore, the fact that some cells were deposited, but not others, is irrelevant.

D. *Enablement of claims 7, 8, 23-27, and 29*

Amgen argues that the district court's holding that GI "provided clear and convincing evidence that the patent specification is insufficient to enable one of ordinary skill in the art to make and use the invention claimed in claim 7 of the '008 patent without undue experimentation" constituted legal error. 13 USPQ2d at 1776. Amgen specifically argues that the district court erred because it "did not properly address the factors which this court has held must be considered in determining lack of enablement based on assertion of undue experimentation," citing this court's decision in *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404.

Claim 7 is a generic claim, covering all possible DNA sequences that will encode any polypeptide having an amino acid sequence "sufficiently duplicative" of EPO to possess the property of increasing production of red blood cells. As claims 8, 23-27, and 29, dependent on claim 7, are not separately argued, and are of similar scope, they stand or fall with claim 7. *See In re Dillon,* 919 F.2d 688, 692, 16 USPQ2d 1897, 1900 (Fed.Cir.1990) (in banc).

[10] Whether a claimed invention is enabled under 35 U.S.C. § 112 is a question of law, which we review *de novo. Moleculon Research Corp. v. CBS, Inc.,* 793 F.2d 1261, 1268, 229 USPQ 805, 811 (Fed.Cir.1986), *cert. denied,*479 U.S. 1030, 107 S.Ct. 875, 93 L.Ed.2d 829 (1987). "To be enabling under § 112, a patent must contain a description that enables one skilled in the art to make and use the claimed invention." *Atlas Powder Co. v. E.I. duPont De Nemours & Co.,* 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed.Cir.1984).

[11] That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however, must not be unduly extensive. *Id.* The essential question here is whether the scope of enablement of claim 7 is as broad as the scope of the claim. *See generally In re Fisher,* 427 F.2d 833, 166 USPQ 18 (CCPA 1970); 2 D. Chisum, *Patents* § 7.03[7][b] (1990).

The specification of the '008 patent provides that:

> one may readily design and manufacture genes coding for microbial expression of polypeptides having primary conformations which differ from that herein specified for mature EPO in terms of the identity or location of one or more residues (e.g., substitutions, terminal and intermediate additions and deletions).
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> * * * * * *
>
> DNA sequences provided by the present invention are thus seen to comprehend all DNA sequences suitable for use in securing expression in a procaryotic***1213** or eucaryotic host cell of a polypeptide product having at least a part of the primary structural conformation and one or more of the biological properties of erythropoietin, and selected from among: (a) the DNA sequences set out in FIGS. 5 and 6; (b) DNA sequences which hybridize to the DNA sequences defined in (a) or fragments thereof; and (c) DNA sequences which, but for the degeneracy of the genetic code, would hybridize to the DNA sequences defined in

(a) and (b).

The district court found that over 3,600 different EPO analogs can be made by substituting at only a single amino acid position, and over a million different analogs can be made by substituting three amino acids. The patent indicates that it embraces means for preparation of "numerous" polypeptide analogs of EPO. Thus, the number of claimed DNA encoding sequences that can produce an EPO-like product is potentially enormous.

In a deposition, Dr. Elliott, who was head of Amgen's EPO analog program, testified that he did not know whether the fifty to eighty EPO analogs Amgen had made "had the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake." Based on this evidence, the trial court concluded that "defendants had provided clear and convincing evidence that the patent specification is insufficient to enable one of ordinary skill in the art to make and use the invention claimed in claim 7 of the '008 patent without undue experimentation." 13 USPQ at 1776. In making this determination, the court relied in particular on the lack of predictability in the art, as demonstrated by the testimony of both Dr. Goldwasser, another scientist who worked on procedures for purifying urinary EPO (uEPO), and Dr. Elliott. After five years of experimentation, the court noted, "Amgen is still unable to specify which analogs have the biological properties set forth in claim 7." *Id.*

[12][13] We believe the trial court arrived at the correct decision, although for the wrong reason. By focusing on the biological properties of the EPO analogs, it failed to consider the enablement of the DNA sequence analogs, which are the subject of claim 7. Moreover, it is not necessary that a patent applicant test all the embodiments of his invention, *In re Angstadt,* 537 F.2d 498, 502, 190 USPQ 214, 218 (CCPA 1976); what is necessary is that he provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims. For DNA sequences, that means disclosing how to make and use enough sequences to justify grant of the claims sought. Amgen has not done that here. In addition, it is not necessary that a court review all the *Wands* factors to find a disclosure enabling. They are illustrative, not mandatory. What is relevant depends on the facts, and the facts here are that Amgen has not enabled preparation of DNA sequences sufficient to support its all-encompassing claims.

[14] It is well established that a patent applicant is entitled to claim his invention generically, when he describes it sufficiently to meet the requirements of Section 112. *See Utter v. Hiraga,* 845 F.2d 993, 998, 6 USPQ2d 1709, 1714 (Fed.Cir.1988) ("A specification may, within the meaning of 35 U.S.C. § 112 ¶ 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses."); *In re Robins,* 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970) ("[R]epresentative samples are not required by the statute and are not an end in themselves."). Here, however, despite extensive statements in the specification concerning all the analogs of the EPO gene that can be made, there is little enabling disclosure of particular analogs and how to make them. Details for preparing only a few EPO analog genes are disclosed. Amgen argues that this is sufficient to support its claims; we disagree. This "disclosure" might well justify a generic claim encompassing these and similar analogs, but it represents inadequate support for Amgen's desire to claim all EPO gene analogs. There may be many other genetic sequences that code for EPO-type products. Amgen has told how to ***1214** make and use only a few of them and is therefore not entitled to claim all of them.

In affirming the district court's invalidation of claims 7, 8, 23-27, and 29 under Section 112, we do not intend to imply that generic claims to genetic sequences cannot be valid where they are of a scope appropriate to the invention disclosed by an applicant. That is not the case here, where Amgen has

claimed every possible analog of a gene containing about 4,000 nucleotides, with a disclosure only of how to make EPO and a very few analogs.

The district court properly relied upon *Fisher* [FN8] in making its decision. In that case, an applicant was attempting to claim an adrenocorticotrophic hormone preparation containing a polypeptide having at least twenty-four amino acids of a specified sequence. Only a thirty-nine amino acid product was disclosed. The court found that applicant could not obtain claims that are insufficiently supported and hence not in compliance with the first paragraph of 35 U.S.C. § 112. It stated:

> FN8. *Cf. Hormone Research Foundation, Inc. v. Genentech, Inc.*, 904 F.2d 1558, 15 USPQ2d 1039 (Fed.Cir.1990). In *Hormone Research*, this court, in a remand, directed the district court to consider the effect of *United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 9 USPQ2d 1461 (Fed.Cir.1989) and *In re Hogan*, 559 F.2d 595, 194 USPQ 527 (CCPA 1977) on *Fisher* in its enablement analysis. The facts of our case are distinguishable from those in *Hormone Research, United States Steel*, and *Hogan*.

> Appellant's parent application, therefore, discloses no products, inherently or expressly, containing other than 39 amino acids, yet the claim includes all polypeptides, of the recited potency and purity, having at least 24 amino acids in the chain in the recited sequence. The parent specification does not enable one skilled in the art to make or obtain ACTHs with other than 39 amino acids in the chain, and there has been no showing that one of ordinary skill would have known how to make or obtain such other ACTHs without undue experimentation. As for appellant's conclusion that the 25th to 39th acids in the chain are unnecessary, it is one thing to make such a statement when persons skilled in the art are able to make or obtain ACTH having other than 39 amino acids; it is quite another thing when they are not able to do so. In the latter situation, the statement is in no way "enabling" and hence lends no further support for the broad claim. We conclude that appellant's parent application is insufficient to support a claim as broad as claim 4.
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> * * * * * *
>
> [Section 112] requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

Fisher, 427 F.2d at 836, 839, 166 USPQ at 21-22, 24.

Considering the structural complexity of the EPO gene, the manifold possibilities for change in its structure, with attendant uncertainty as to what utility will be possessed by these analogs, we consider that more is needed concerning identifying the various analogs that are within the scope of the claim, methods for making them, and structural requirements for producing compounds with EPO-like activity. It is not sufficient, having made the gene and a handful of analogs whose activity has not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity. Under the circumstances, we find no error in the court's conclusion that the generic DNA sequence claims are invalid under Section 112.

E. *Inequitable Conduct*

Defendants argue that the '008 patent claims are unenforceable as a result of an asserted misrepresentation of the number of probes Lin used for the monkey gene cloning described in Example 3 of his patent. Relying on the district court's finding that Lin had said that a "full set" mixture of 128 "EpV" probes [FN9] was used for monkey cDNA screening, whereas only a 16-member "subset" of the EpV mixture was actually used, defendants argue that the ***1215** court ought to have found that the representations were material.

FN9. The probes designated "EpV" were from EPO amino acid sequence region 46-52.

[15][16] The essential elements of proof of inequitable conduct include intent to deceive and materiality. After finding threshold levels of materiality and intent, the trial court must balance the two and determine, in its discretion, whether inequitable conduct has occurred. *J.P. Stevens & Co. v. Lex Tex Ltd., Inc.*, 747 F.2d 1553, 1560, 223 USPQ 1089, 1092 (Fed.Cir.1984), *cert. denied*,474 U.S. 822, 106 S.Ct. 73, 88 L.Ed.2d 60 (1985). While we review an ultimate conclusion of inequitable conduct under an abuse of discretion standard, *Kingsdown Medical Consultants, Ltd. v. Hollister Inc.*, 863 F.2d 867, 876, 9 USPQ2d 1384, 1392 (Fed.Cir.1988) (in banc), *cert. denied*,490 U.S. 1067, 109 S.Ct. 2068, 104 L.Ed.2d 633 (1989), the underlying factual threshold findings are reviewed under a clearly erroneous standard.

[17] Lin set out to clone the EPO gene by more than one method, including using degenerate human probes and monkey probes. It is not disputed that he did isolate the human EPO gene from a genomic library using two different 128-member pools of probes made from fragments of the human EPO protein. Thereafter, he also attempted to use the human sequence probes to find the monkey EPO cDNA to be used later as a probe to hybridize with the human EPO gene. Example 3 of the '008 patent describes this work, indicating that the screening yielded seven positive clones. It also reports that a subset of the human EpV mixture was used for DNA sequencing work. When Lin published his monkey cDNA cloning work in a scientific journal, he also reported the use of 128 EpV probes to screen the monkey library. Lin screened the monkey library with the full mixture of 128 EpV probes and with one of eight subsets of probes which made up the full EpV mixture. In response to a question whether a subset of EpV probes was used in the first screening of the monkey cDNA library, Lin testified:

> I don't know which we used, the subset first or used the full set first. I cannot recall exactly. It looks like the subset was first defining the number, yes.

This answer constituted the sole basis for the court's finding that, "[a]t trial, Lin admitted he only used a subset of the EpV 128 probes in screening the cDNA library." 13 USPQ2d at 1778.

We consider that the district court's finding of an "admission" of misrepresentation in Lin's testimony and its conclusion that GI "presented clear and convincing evidence of a misrepresentation" was clearly erroneous. That Lin did not recall whether he first screened the monkey cDNA library with a full set of probes or a subset of probes, and his answer that "it looks like" he used the subset, are certainly not clear admissions that he only used a subset. However, the district court was correct in concluding that, even if there had been an erroneous statement, it was not material because Lin succeeded in cloning the EPO gene first with his use of the fully-degenerate probes. Thus, his testimony does not provide clear and convincing evidence that he misrepresented to the PTO the number of probes used. He did use 128-member probes as well as a subset. Moreover, this evidence does not create an inference of an intent to mislead. The court properly concluded that there was no inequitable conduct in prosecuting the '008 patent.

II. GI's '195 PATENT (Hewick)

A. *Enablement of claims 1 and 3*

Amgen challenges the district court's determination that "the '195 patent enables a person of ordinary skill in the art to obtain homogeneous EPO [including rEPO and uEPO] from natural sources" having a mean *in vivo* specific activity of at least 160,000.[FN10] 13 USPQ2d at 1794. Claims 1 and 3 contain the limitation that EPO have a specific activity of at least 160,000 ***1216** IU/AU. The district court found, based upon expert testimony from both sides, that to those skilled in the art, in the ab-

sence of an express statement in the patent, the claims would be construed to refer to *in vivo* rather than *in vitro* specific activity. To support its challenge, Amgen asserts that the district court's determination is contradicted by GI's own bioassay data and by the district court's finding that "the '195 patent fails to enable the purification of rEPO." Amgen also asserts that the district court erred in relying solely on an *in vitro* measure of specific activity, having initially construed the '195 claims as requiring an *in vivo* measure to avoid invalidity for indefiniteness.

> FN10. The potency of EPO in the '195 patent is stated as its specific activity, expressed as a ratio of International Units (which measures the ability of EPO to cause formation of red blood cells) per absorbance unit (the amount of light absorbed by a sample of EPO measured by a spectrophotometer at a given wavelength, 280 nanometers), *i.e.*, IU/AU.

35 U.S.C. § 112 requires that an invention be described "in such full, clear, concise, and exact terms as to enable any person skilled in the art ... to make and use the same." We review a determination of enablement as a question of law. *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1268, 229 USPQ 805, 811 (Fed.Cir.1986), *cert. denied*,479 U.S. 1030, 107 S.Ct. 875, 93 L.Ed.2d 829 (1987).

[18] We do not consider the court's finding that the assay measurement was an *in vivo* one to be erroneous in view of the testimony it heard. That being the case, the question is whether the court erred in concluding that the claims requiring 160,000 IU/AU by an *in vivo* measurement were enabled. We conclude that it did err.

Defendants have produced no evidence that it ever prepared EPO with a specific activity of at least 160,000 IU/AU *in vivo* using the disclosed methods. In its report to the FDA, GI stated that it had purified uEPO material "to homogeneity" by subjecting partially purified uEPO material to reverse phase high performance liquid chromatography (RP-HPLC), the technique taught by Hewick in the '195 patent. The district court found that GI reported to the FDA that the specific activity of uEPO, based on *in vivo* bioassays, was only 109,000 IU/AU.[FN11] GI originally arrived at the figure of 160,000 IU/AU by calculation, before it had the capacity to derive quantitative information from bioassays. Hewick subjected the EPO to RP-HPLC, the EPO having an actual value of 83,000 IU/AU. After weighing the chromatograph, he found that "at least fifty percent" of the area under the chromatograph curve was attributable to something other than EPO. He then doubled the 83,000, and arrived at a theoretical specific activity of "at least about 160,000 IU/AU." That procedure, while possibly valid as a means for estimating the specific activity of a pure sample, does not establish that GI had a workable method for actually obtaining the pure material that it claimed.

> FN11. Defendants provided no evidence that faulty purification procedures or other missteps caused its failure to obtain 160,000 IU/AU *in vivo* material as claimed in the '195 patent.

Moreover, the work of others shows that Hewick did not enable the preparation of uEPO having an *in vivo* specific activity of at least 160,000, as the claims required. Dr. Kawakita, a scientist at Kummamoto University in Japan, reported an *in vivo* specific activity of 101,000 IU/AU when using RP-HPLC according to Hewick's method. This is similar to the 109,000 value reported to the FDA by GI. Kawakita did report a value of 188,000, but did not follow the teachings in the '195 patent. Defendants also rely on the testimony of Fritsch that "I've also seen further data in Chugai's PLA indicating additional urinary EPO preparation that had activities of 190,000, I believe, units per absorbance unit." However, the document to which Fritsch referred was not offered into evidence by GI after Amgen objected to its introduction and is not be-

fore us.

Defendants argue that Dr. Kung's uEPO test result of 173,640 IU/AU in an *in vitro* test supports the enablement of its claims. Amgen argues that an *in vivo* test result would only have been 65 percent of the *in vitro* result and thus would not have met the 160,000 IU/AU limitation of the claims. The district court relied on Kung, despite the demonstrated disparity between the results of *in vitro* and *in vivo* testing.

It is not absolutely clear to us that, for uEPO, the *in vivo* specific activity is 65 percent of the *in vitro* specific activity. ***1217** Nonetheless, Kung's measurement, being *in vitro*, does not demonstrate enablement of the claimed invention, and that fact means that the court erred in finding enablement. Added to this fact is the difference that exists between the *in vivo* results for rEPO and uEPO [FN12], and the other lack of support for the 160,000 limitation. Under these circumstances, we hold that the district court erred in accepting the *in vitro* data as support for claims containing what has been found to be an *in vivo* limitation.

> FN12. The court quoted Chugai to the effect that the *in vivo* activity of uEPO is 65 percent that of rEPO.

In addition to the question of enablement regarding uEPO, the district court found that the only purification attempt on rEPO in the manner set out in the '195 patent failed to provide homogeneous EPO. The patent itself, in Example 2, discloses GI's purification efforts on rEPO and indicates that GI did not obtain purified rEPO. As the district court found, "[t]he patent does not contain any procedures ... for purifying rEPO to the point that RP-HPLC will be successful." 13 USPQ2d at 1758. Thus, the patent fails to enable purification of either rEPO or uEPO.[FN13] *See In re Rainer*, 377 F.2d 1006, 1012, 153 USPQ 802, 807, 54 CCPA 1445 (1967) ("specification is evidence of its own inadequacy").

> FN13. Chugai's sample reported to the Food and Drug Administration was not purified by the disclosed process.

The burden of showing non-enablement is Amgen's, not GI's, but in the case of a challenged patent, when substantial discovery has occurred, and there is no credible evidence that the claimed purified material can be made by those skilled in the art by the disclosed process, and all evidence from both the inventor and his assignee and from third parties is to the contrary, we conclude that Amgen has met its burden to show that the claims have not been adequately enabled. We do not hold that one must always prove that a disclosed process operates effectively to produce a claimed product. But, under these circumstances, we conclude that the court erred in holding that claims 1 and 3 were properly enabled.

B. *Indefiniteness of claims 4 and 6*

The district court held claims 4 and 6 of the '195 patent invalid because their specific activity limitation of "at least about 160,000" was indefinite. Defendants challenge this holding, asserting that there is no evidence that claims 4 and 6 do not comply with the requirements of 35 U.S.C. § 112.

[19][20] The statute requires that "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." A decision as to whether a claim is invalid under this provision requires a determination whether those skilled in the art would understand what is claimed. *See Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed.Cir.1985) (Claims must "reasonably apprise those skilled in the art" as to their scope and be "as precise as the subject matter permits."). The district court found that "bioassays provide an imprecise form of measurement with a range of error" and that use of the term "about" 160,000 IU/AU, coupled with the range of error

already inherent in the specific activity limitation, served neither to distinguish the invention over the close prior art (which described preparations of 120,000 IU/AU), nor to permit one to know what specific activity values below 160,000, if any, might constitute infringement. 13 USPQ2d at 1787. It found evidence of ambiguity in the fact that Chugai, GI's partner, itself questioned whether the specific activity value of 138,000 IU/AU for its own rEPO was within the claim coverage.

In prosecuting the '195 patent, GI disclosed to the examiner a publication by Miyake et al., which discloses a uEPO product having an *in vivo* specific activity of 128,620 IU/AU. When the examiner noticed this disclosure late in the prosecution, he rejected the '195 claims with a specific activity limitation of "at least 120,000" as anticipated by the Miyake et al. disclosure. ***1218** It was only after the "at least 120,000" claims were cancelled that GI submitted the "at least about 160,000" claim language.

The court found the "addition of the word 'about' seems to constitute an effort to recapture ... a mean activity somewhere between 120,000, which the patent examiner found was anticipated by the prior art, and [the] 160,000 IU/AU" claims which were previously allowed. Because "the term 'about' 160,000 gives no hint as to which mean value between the Miyake et al. value of 128,620 and the mean specific activity level of 160,000 constitutes infringement," the court held the "at least about" claims to be invalid for indefiniteness. 13 USPQ2d at 1787-88. This holding was further supported by the fact that nothing in the specification, prosecution history, or prior art provides any indication as to what range of specific activity is covered by the term "about," and by the fact that no expert testified as to a definite meaning for the term in the context of the prior art. In his testimony, Fritsch tried to define "about" 160,000, but he could only say that while "somewhere between 155[,000] might fit within that number," he had not "given a lot of direct considerations to that...."

[21] When the meaning of claims is in doubt, especially when, as is the case here, there is close prior art, they are properly declared invalid. *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 453, 227 USPQ 293, 297 (Fed.Cir.1985). We therefore affirm the district court's determination on this issue. We also note that, in view of our reversal of the district court's holding that claims 1 and 3 are valid, it is clear that claims 4 and 6 would also be invalid without the "about" limitation. In arriving at this conclusion, we caution that our holding that the term "about" renders indefinite claims 4 and 6 should not be understood as ruling out any and all uses of this term in patent claims. It may be acceptable in appropriate fact situations, *e.g., W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1557, 220 USPQ 303, 316 (Fed.Cir.1983) ("use of 'stretching ... at a rate exceeding about 10% per second' in the claims is not indefinite"), even though it is not here.

C. *Inequitable Conduct*

The district court concluded that GI did not engage in inequitable conduct with respect to the '195 patent. Amgen challenges this holding, asserting, *inter alia,* that GI displayed an intent to mislead by withholding data showing *in vivo* specific activity of homogenous uEPO and withholding information on the range of error in EPO bioassays.

[22][23][24] It is fundamental that to establish inequitable conduct, an intent to deceive is required. *RCA Corp. v. Data General Corp.*, 887 F.2d 1056, 1065, 12 USPQ2d 1449, 1456-57 (Fed.Cir.1989). A finding of an intent to deceive may follow from an assessment of materiality, knowledge, and surrounding circumstances, including evidence of good faith. *Kingsdown Medical Consultants Ltd. v. Hollister Inc.*, 863 F.2d 867, 876, 9 USPQ2d 1384, 1392 (Fed.Cir.1988), *cert. denied,*490 U.S. 1067, 109 S.Ct. 2068, 104 L.Ed.2d 633 (1989). The district court found no such intent, stating:

the record is devoid of any evidence that would es-

> tablish deliberate knowing withholdings of any kind by Dr. Hewick or GI. Dr. Hewick was a credible witness who spoke carefully and candidly about his work ... There is no evidence that Dr. Hewick withheld any information he believed was material to the patent examiner.

Amgen, 13 USPQ2d at 1791. There is no clear error in this finding. Amgen raises no inequitable conduct issues that were not fully considered by the district court. We have reviewed the record and find no abuse of discretion on the part of the district court. This is also not an exceptional case.

III. OTHER ISSUES

In view of our conclusion that the district court erred as a matter of law in holding that claims 1 and 3 of the '195 patent are not invalid, we vacate the district court's holdings relating to infringement of those ***1219** claims. We have considered the other arguments by counsel on both sides and find them to be without merit.

CONCLUSION

We conclude that the district court did not err in its findings that claims 2, 4, and 6 of the '008 patent are valid and enforceable and have been infringed by GI, and that claims 7, 8, 23-27, and 29 of the '008 patent are invalid; we therefore affirm the judgment of the court regarding the '008 patent. Because we conclude that claims 1, 3, 4, and 6 of the '195 patent are invalid, we affirm the judgment concerning claims 4 and 6 and reverse the judgment concerning claims 1 and 3.

COSTS

Each party shall bear its own costs.

AFFIRMED-IN-PART, REVERSED-IN-PART, VACATED-IN-PART.

C.A.Fed. (Mass.),1991.

Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.
927 F.2d 1200, 59 USLW 2575, 18 U.S.P.Q.2d 1016

END OF DOCUMENT

Exhibit 8

United States Court of Appeals,
Federal Circuit.
EISAI CO. LTD. and Eisai, Inc., Plaintiffs-Appellees,
v.
DR. REDDY'S LABORATORIES, LTD. and Dr. Reddy's Laboratories, Inc., Defendants-Appellants,
and
Teva Pharmaceuticals USA, Inc., Defendant-Appellant.
Nos. 2007-1397, 2007-1398.

July 21, 2008.
Rehearing and Rehearing En Banc Denied Sept. 16, 2008.

Background: Patentee of patent claiming lead compound used in pharmaceutical approved for the treatment of duodenal ulcers, heartburn, and associated disorders brought infringement action against competitors. The United States District Court for the Southern District of New York, Gerard E. Lynch, J., 472 F.Supp.2d 493, 2006 WL 2872615, granted in part and denied in part owner's motions for summary judgment, and found competitors infringed patent. Competitors appealed.

Holdings: The Court of Appeals, Rader, Circuit Judge, held that:
(1) prior art did not render patent obvious, and
(2) patentee did not commit inequitable conduct in prosecuting patent application for patent.

Affirmed.

West Headnotes

[1] Patents 291 ⚿16.13

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.13 k. Fact Questions. Most Cited Cases
Obviousness, for patent law purposes, is ultimately a legal question, based on underlying factual determinations. 35 U.S.C.A. § 103(a).

[2] Patents 291 ⚿16(2)

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16 Invention and Obviousness in General
291k16(2) k. Prior Art in General. Most Cited Cases

Patents 291 ⚿16(3)

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16 Invention and Obviousness in General
291k16(3) k. View of Person Skilled in Art. Most Cited Cases

Patents 291 ⚿36.1(1)

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k36 Weight and Sufficiency
291k36.1 Secondary Factors Affecting Invention or Obviousness
291k36.1(1) k. In General. Most Cited Cases
The factual determinations underpinning the legal conclusion of obviousness, for patent law purposes, include: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) evidence of secondary factors, also known as objective indicia of non-obviousness. 35 U.S.C.A. § 103(a).

[3] Patents 291 ⚿324.5

291 Patents
291XII Infringement
291XII(C) Suits in Equity
291k324 Appeal
291k324.5 k. Scope and Extent of Review in General. Most Cited Cases
In reviewing a district court's summary judgment of non-obviousness in a patent infringement proceeding, the appellate court reviews the record for genuine issues of material fact without deference, bearing in mind the movant's burden to prove invalidity by clear and convincing evidence. 35 U.S.C.A. § 103(a).

[4] Patents 291 ⚿16.25

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.25 k. Chemical Compounds. Most Cited Cases
Where the patent at issue claims a chemical compound, the analysis of the third *Graham* factor for determining obviousness, the differences between the claimed invention and the prior art, often turns on the structural similarities and differences between the claimed compound and the prior art compounds; obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound in a particular way to achieve the claimed compound. 35 U.S.C.A. § 103(a).

[5] Patents 291 ⚿16.25

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.25 k. Chemical Compounds. Most Cited Cases
The requisite motivation to prove the obviousness of a patent claiming a chemical compound based on structural similarity can come from any number of sources and need not necessarily be explicit in the art; rather it is sufficient to show that the claimed and prior art compounds possess a sufficiently close relationship to create an expectation, in light of the totality of the prior art, that the new compound will have similar properties to the old. 35 U.S.C.A. § 103(a).

[6] Patents 291 ⚿16.25

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.25 k. Chemical Compounds. Most Cited Cases
Prior art did not render obvious patent claiming lead compound used in pharmaceutical approved for the treatment of duodenal ulcers, heartburn, and associated disorders, where compounds claimed by prior art differed structurally from compound claimed by patent, and the record contained no reasons a skilled artisan would have considered the differences between the compounds identifiable and predictable. 35 U.S.C.A. § 103(a).

[7] Patents 291 ⚿324.54

291 Patents
291XII Infringement
291XII(C) Suits in Equity
291k324 Appeal
291k324.54 k. Presumptions and Discretion of Lower Court. Most Cited Cases

Patents 291 ⚿324.55(2)

291 Patents
291XII Infringement
291XII(C) Suits in Equity
291k324 Appeal
291k324.55 Questions of Fact, Verdicts, and Findings
291k324.55(2) k. Clearly Erroneous Findings. Most Cited Cases
Where a judgment regarding inequitable conduct in prosecuting a patent application follows a bench trial, the appellate court reviews the district court's findings of materiality and intent for clear error and its ultimate conclusion for an abuse of discretion.

[8] Patents 291 ⚿97

291 Patents

291IV Applications and Proceedings Thereon
291k97 k. Patent Office and Proceedings Therein in General. Most Cited Cases
Inequitable conduct in prosecuting a patent application before the Patent and Trademark Office (PTO) may take the form of an affirmative misrepresentation of material fact, a failure to disclose material information, or the submission of false material information, but in every case this false or misleading material communication or failure to communicate must be coupled with an intent to deceive; "materiality," defined as "what a reasonable examiner would have considered important in deciding whether to allow a patent application," and intent are both questions of fact, and require proof by clear and convincing evidence.

[9] Patents 291 ⚿97

291 Patents
291IV Applications and Proceedings Thereon
291k97 k. Patent Office and Proceedings Therein in General. Most Cited Cases
To satisfy the "intent" prong for unenforceability of a patent due to inequitable conduct during the prosecution of a patent application, the involved conduct, viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive; gross negligence is not sufficient.

[10] Patents 291 ⚿97

291 Patents
291IV Applications and Proceedings Thereon
291k97 k. Patent Office and Proceedings Therein in General. Most Cited Cases
Patentee did not commit inequitable conduct in prosecuting patent application for patent claiming lead compound used in pharmaceutical approved for the treatment of duodenal ulcers, heartburn, and associated disorders by failing to disclose its own co-pending application, withholding rejections from its co-pending application that also would have applied to patent, failing to disclose prior art, submitting a misleading declaration, and concealing similar compound, where record lacked sufficient evidence of intent to deceive.

Patents 291 ⚿328(2)

291 Patents
291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents
291k328 Patents Enumerated
291k328(2) k. Original Utility. Most Cited Cases
4,255,431. Cited as Prior Art.

Patents 291 ⚿328(2)

291 Patents
291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents
291k328 Patents Enumerated
291k328(2) k. Original Utility. Most Cited Cases
5,045,552. Infringed.
***1355** Joseph M. O'Malley, Jr., Paul, Hastings, Janofsky & Walker, LLP, of New York, New York, argued for plaintiffs-appellees. With him on the brief were Bruce M. Wexler, David M. Conca, Gary G. Ji, and Quinn E. Clancy.

Maurice N. Ross, Budd Larner, P.C., of Short Hills, New Jersey, argued for defendants-appellants Dr. Reddy's Laboratories, Ltd., and Dr. Reddy's Laboratories, Inc. With him on the brief were Andrew J. Miller, Louis H. Weinstein, Ellen T. Lowenthal, and Dmitry V. Sheluho.

Henry C. Dinger, Goodwin Procter LLP, of Boston, Massachusetts, argued for defendant-appellant Teva Pharmaceuticals USA, Inc. With him on the brief were Elaine H. Blais, and David M. Hashmall, Frederick H. Rein, and Emily L. Rapalino, of New York, New York.

Before RADER, LINN, and PROST, Circuit Judges.

RADER, Circuit Judge.

On summary judgment, the United States District Court for the Southern District of New York found in favor of plaintiffs Eisai Co., Ltd. and Eisai, Inc. (collectively Eisai) with respect to the validity and en-

forceability of U.S. Patent No. 5,045,552 ('552 patent). *Eisai Co. v. Teva Pharms. USA, Inc.*, 472 F.Supp.2d 493 (S.D.N.Y.2006) (*SJ Validity Order*); *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, No. 03 Civ. 9053 (S.D.N.Y. Oct. 5, 2006) (*SJ Enforceability Order*). After a bench trial, the district court found that Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (collectively Dr. Reddy's) and Teva Pharmaceuticals USA, Inc. (Teva) had failed to prove the remaining allegations of inequitable conduct, and that Eisai had established that Dr. Reddy's and Teva infringed Eisai's '552 patent. *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, No. 03 Civ. 9053, 2007 WL 1406565 (S.D.N.Y. May 11, 2007) (*Trial Order*). Because the district court correctly determined that the '552 patent is non-obvious over the proffered prior art and that Eisai's alleged acts during prosecution did not rise to the level of inequitable conduct, this court affirms.

***1356** I

The '552 patent claims rabeprazole and its salts. Rabeprazole is part of a class of drugs known as proton pump inhibitors, which suppress gastric acid production by inhibiting action of the enzyme H^+K^+ATPase. The distinctions between rabeprazole and its salts are not relevant for this appeal. Therefore this court refers to rabeprazole and its salts collectively as "rabeprazole." Rabeprazole's sodium salt is the active ingredient in Aciphex, a pharmaceutical approved in 1991 by the FDA for the treatment of duodenal ulcers, heartburn, and associated disorders. Aciphex has been a commercial success, garnering over $1 billion in worldwide yearly sales.

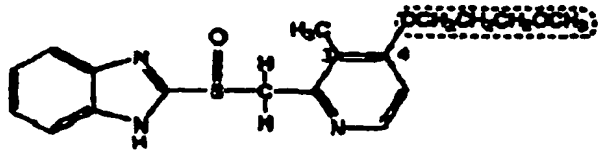
Dr. Reddy's and Teva each filed Abbreviated New Drug Applications (ANDAs) under the Hatch-Waxman Act, 21 U.S.C. § 355 and 35 U.S.C. § 271(e), seeking to manufacture a generic version of Aciphex before the expiration of the '552 patent. Because filing an ANDA is an artificial, but legally cognizable, act of patent infringement, *see Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1344 (2004), Eisai filed suit against Dr. Reddy's and Teva. Eisai also sued Mylan Laboratories Inc. and Mylan Pharmaceuticals Inc. (collectively Mylan), another ANDA filer, but that proceeding was stayed pending the outcome of these actions. Mylan agreed to be bound by the final judgments and any appeals in these cases. *Eisai Co., Ltd. v. Mylan Labs., Inc.*, No. 04 Civ. 656 (S.D.N.Y. Nov. 3, 2004). Both Dr. Reddy's and Teva conceded infringement of claims 1-6 of the '552 patent, but asserted that the '552 patent is unenforceable for inequitable conduct. *Trial Order* at 6-7. Dr. Reddy's stipulated to the validity of all six of the '552 patent's claims, *id.* at 6, but Teva argued before the district court and maintains on appeal that the '552 patent is invalid for obviousness. Both Dr. Reddy's and Teva appeal the trial court's judgments of enforceability. Neither Dr. Reddy's nor Teva appeals the trial court's judgment of infringement. This court has jurisdiction under 28 U.S.C. § 1295(a)(1).

II

[1][2][3] This court reviews a grant of summary judgment without deference. *Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1362 (Fed.Cir.2003). Obviousness under 35 U.S.C. § 103(a) is ultimately a legal question, based on underlying factual determinations. *See Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed.Cir.1997). The factual determinations underpinning the legal conclusion of obviousness include 1) the scope and content of the prior art, 2) the level of ordinary skill in the art, 3) the differences between the claimed invention and the prior art, and 4) evidence of secondary factors, also known as objective indicia of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966). Thus, in reviewing a district court's summary judgment of non-obviousness, this court reviews the record for genuine issues of material fact without deference, bearing in mind the movant's burden to prove invalidity by clear and convincing evidence. *See Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed.Cir.1998).

[4][5] Where, as here, the patent at issue claims a chemical compound, the analysis of the third *Graham* factor (the differences between the claimed invention and the prior art) often turns on the structural similarities and differences between the claimed compound and the prior art ***1357** compounds. *See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1377 (Fed.Cir.2006) (noting that, for a chemical compound, a prima facie case of obviousness requires "structural similarity between claimed and prior art

subject matter ... where the prior art gives reason or motivation to make the claimed compositions" (quoting *In re Dillon*, 919 F.2d 688, 692 (Fed.Cir.1990) (en banc))). Obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound. *See Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed.Cir.2007). In keeping with the flexible nature of the obviousness inquiry, *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S.Ct. 1727, 1739, 167 L.Ed.2d 705 (2007), the requisite motivation can come from any number of sources and need not necessarily be explicit in the art. *See Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed.Cir.2007). Rather "it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship ... to create an expectation,' in light of the totality of the prior art, that



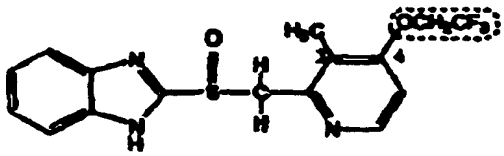
Rabeprazole

Appellant Teva's Br. at 28. Otherwise, the two compounds are identical. *See SJ Validity Order* at 7. Both rabeprazole and lansoprazole are "asymmetrically substituted" with respect to the 4-position on the pyridine ring because the substituent at the 3-position (a methyl group in both compounds) is not the same as the substituent at the 5-position (a hydrogen in both compounds).

The '431 patent discloses a broad class of gastric acid inhibiting compounds, including omeprazole, the first commercial proton pump inhibitor, sold as Prilosec. Although sharing the same basic structure, omeprazole is structurally farther afield from rabeprazole than is lansoprazole. For instance, omeprazole's pyridine ring is symmetrically substituted and has a methoxy (OCH3) group at the 4-position.

the new compound will have 'similar properties' to the old." *Id.* (quoting *Dillon*, 919 F.2d at 692).

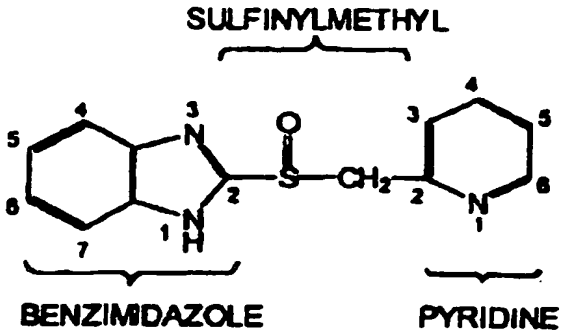
[6] Teva asserts that a combination of three prior art references renders the '552 patent obvious: 1) European Patent No. 174,726 (owned by Takeda), claiming lansoprazole (EP '726); 2) United States Patent No. 4,255,431 (to Junggren), claiming omeprazole ('431 patent); and 3) an article by Brändström, et al., entitled "Structure Activity Relationships of Substituted Benzimidazoles" (Brändström). EP '726 teaches, inter alia, the ulcer treatment le. Lansoprazole differs structurally from rabeprazole at the 4-position on the pyridine ring, as indicated in the diagram below. Lansoprazole has a trifluoroethoxy (OCH_2CF_3) substituent, whereas rabeprazole has a methoxypropoxy ($OCH_2CH_2CH_2\ OCH_3$) substituent.



Lansoprazole

Finally, Brändström describes a class of anti-ulcerative compounds having a benzimidazole-sulfinylmethyl-pyridine core (the Brändström core structure):

***1358**



Brändström Core Structure

Rabeprazole, lansoprazole, and omeprazole are all Brändström core structure compounds. Taking the evidence in the light most favorable to Teva, this court assumes that as per EP '726, lansoprazole is twenty times superior to omeprazole for anti-ulcer action, as measured by an indomethacin-induced gastric lesion assay in rats. This court also assumes that lansoprazole has certain traits, including lipophilicity (the ability of a compound to cross lipid membranes) and low molecular weight, that would have made it desirable to a skilled artisan.

Under these assumptions, one of skill in this art may have considered it a candidate for a lead compound in the search for anti-ulcer compounds. To the contrary, the district court emphasized the differences between anti-ulcer action and gastric acid inhibition. The trial court specifically noted that Teva's expert testified with respect to the EP '726 data that "[t]he level of acid secretion ... from these [anti-ulcer] data ... cannot be determined." *SJ Validity Order* at 13. In this context, this court consults the counsel of *KSR* that "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." 127 S.Ct. at 1742. Thus lansoprazole's candidacy as a starting point to develop new anti-ulcer compounds versus new gastric acid inhibitors does not resolve the lead compound analysis, at least not in the absence of any contrary indications. *Cf. Takeda*, 492 F.3d at 1359 (negative side effects could dissuade one of skill from using a particular compound as a starting point).

Nonetheless, as the district court noted, the EP '726 reference teaches at best that the fluorinated substituent of lansoprazole provides "a *special path* to achieving lipophilicity." *SJ Validity Order* at 10 (emphasis in original). And Teva's expert identified a separate reference teaching that fluorine-substituted groups increase lipophilicity. *Id.* The record, however, shows no discernible reason for a skilled artisan to begin with lansoprazole only to drop the very feature, the fluorinated substituent, that gave this advantageous property. Indeed, Teva's pharmacology expert, Dr. John Forte, declined to opine on lansoprazole's relevance to an examiner assessing the patentability of rabeprazole. J.A. at 14894. And Dr. Reddy's pharmacology expert, Dr. Simmy Bank, testified in deposition that "I thought [lansoprazole] had nothing to do with this trial." J.A. at 14756.

This court notes that the district court did not rigidly limit Teva's obviousness arguments by forcing Teva to select a single lead compound. Rather Teva alone ***1359** selected lansoprazole as the anchor for its obviousness theory, not the district court. In *KSR*, the Supreme Court noted that an invention may have been obvious "[w]hen there [was] ... a design need or market pressure to solve a problem and there [were] ... a finite number of identified, predictable solutions." 127 S.Ct. at 1742 (tense changes supplied to clarify, as the Court stated and as per 35 U.S.C. § 103, that the obviousness inquiry must rely on evidence available "at the time" of the invention, *see Takeda*, 492 F.3d at 1356 n. 2). The Supreme Court's analysis in *KSR* thus relies on several assumptions about the prior art landscape. First, *KSR* assumes a starting reference point or points in the art, prior to the time of

invention, from which a skilled artisan might identify a problem and pursue potential solutions. Second, *KSR* presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. *See Takeda*, 492 F.3d at 1357 ("Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."). Third, the Supreme Court's analysis in *KSR* presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions," 127 S.Ct. at 1742. In *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364 (Fed.Cir.2008), this court further explained that this "easily traversed, small and finite number of alternatives ... might support an inference of obviousness." To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.

In other words, post- *KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound. Teva cannot create a genuine issue of material fact on obviousness through the unsupported assertion that compounds other than lansoprazole might have served as lead compounds. Further, the record contains no reasons a skilled artisan would have considered modification of lansoprazole by removing the lipophilicity-conferring fluorinated substituent as an identifiable, predictable solution. In sum, the district court properly concluded that the record did not support a case of obviousness of the '552 patent as a matter of law.

III

[7] As with other summary judgment issues, this court reviews a district court's summary judgment on inequitable conduct without deference. *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1378 (Fed.Cir.2008). In contrast, where a judgment regarding inequitable conduct follows a bench trial, this court reviews the district court's findings of materiality and intent for clear error and its ultimate conclusion for an abuse of discretion. *ACCO Brands, Inc. v. ABA Locks Mfrs. Co.*, 501 F.3d 1307, 1314 (Fed.Cir.2007).

[8][9] Inequitable conduct in prosecuting a patent application before the United States Patent & Trademark Office may take the form of an affirmative misrepresentation of material fact, a failure to disclose material information, or the submission***1360** of false material information, but in every case this false or misleading material communication or failure to communicate must be coupled with an intent to deceive. *Innogenetics*, 512 F.3d at 1378 (citations omitted). Materiality, defined as "what a reasonable examiner would have considered important in deciding whether to allow a patent application," and intent are both questions of fact, and require proof by clear and convincing evidence. *Id.* To satisfy the "intent" prong for unenforceability, "the involved conduct, viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive." *Kingsdown Med. Consultants, Ltd. v. Hollister Inc.*, 863 F.2d 867, 876 (Fed.Cir.1988) (en banc) (citing *Norton v. Curtiss*, 57 C.C.P.A. 1384, 433 F.2d 779 (1970)). Gross negligence is not sufficient. *Id.* This is a high bar.

[10] On appeal, Teva and Dr. Reddy's allege that Eisai misled the Patent Office in five ways: 1) failing to disclose Eisai's own co-pending '013 application, which claimed the "ethyl homolog" of rabeprazole (compound SHKA 661); 2) withholding rejections from the '013 application's prosecution that also would have been applicable to the '552 patent's prosecution; 3) failing to disclose the prior art "Byk Gulden patent" (WO 8602646); 4) submitting a misleading declaration (the Fujisaki Declaration) to the examiner of the '552 patent; and 5) concealing lansoprazole from the examiner. The district court rejected the fifth assertion on summary judgment, *SJ Enforceability Order* at 58, and the other four after a bench trial, *Trial Order*.

Teva and Dr. Reddy's first and second allegations rely on Eisai's failure to disclose the fact of, and rejections contained in, Eisai's patent application claiming the "ethyl homolog" of rabeprazole. Known to Eisai's

scientists as compound SHKA 661, the ethyl homolog differs from rabeprazole as its name suggests. SHKA 661 has one fewer methylene unit at the 4-position of the pyridine ring, giving SHKA 661 an ethoxy group rather than a propoxy group at this position. The district court correctly pointed out that calling SHKA 661 the "ethyl homolog" of rabeprazole in this case could carry a misleading implication with respect to inequitable conduct. The record supplies no evidence to suggest that Eisai's scientists ever referred to SHKA 661 by this name, or thought of SHKA 661 and rabeprazole "primarily in relation to each other." *Trial Order* at 17 n. 7. Rather, the district court found credible the testimony that Eisai scientists considered SHKA 661 separately patentable, even though Eisai ultimately did not pursue that course. *Id.* at 22-23; 42-43. Furthermore, even if a provisional obviousness-type double-patenting rejection might have issued in the prosecution of the '552 patent due to the co-pending SHKA 661 application, the district court found the materiality of this potential situation low, because applicants routinely overcome this type of rejection, *id.* at 44, by amending claims or filing a terminal disclaimer. Nonetheless, the district court did not hold that the fact of the copendency of these two applications to be totally immaterial, accurately noting that applicants should be encouraged to disclose closely related applications. *Id.* at 47.

While disclosure of the co-pending SHKA 661 application to the Patent Office during the prosecution of the '552 patent would have been prudent, Eisai's failure to do so is by no means fatal, for two reasons. First, the district court had ample evidence from which to conclude that the materiality of the SHKA 611 application ***1361** was low, as outlined above. Second, the record is devoid of any real suggestion of intent to deceive the Patent Office, much less the clear and convincing evidence required to support a finding of inequitable conduct.

As for the rejections of the '013 application that would have been relevant to the prosecution of the '552 patent, the district court did not reach materiality because it discerned insufficient proof of intent to deceive. The district court found the documentary evidence (faxed exchange between Eisai employees Mr. Shuhei Miyazawa, one of the inventors of the '552 patent, and Mr. Mitsuo Taniguchi, Eisai's patent agent, regarding Mr. Miyazawa's presentation to a pharmaceutical trade industry group) to supply no compelling evidence of intent, based on testimony from both parties to the fax. Witness credibility determinations lie squarely within the district court's discretion. *See Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1171 (Fed.Cir.2006). The district court was ultimately undisturbed by the Taniguchi/Miyazawa communication based on its evaluation of the witness testimony presented, and this court sees no abuse of discretion. These facts certainly do not rise to the level of "culpability" this court required in *Kingsdown*, 863 F.2d at 876, to establish intent to deceive, or even gross negligence.

Finally, the district court found that Teva's theory that Eisai deliberately hid the ball from the Patent Office by separately filing the '552 and '013 prosecutions to be "implausibly risky," given that such similar applications would usually be assigned to the same examiner in the same art unit. *Trial Order* at 53. The district court thus had ample bases from which to conclude that Eisai's failure to disclose its co-pending '013 application along with the rejections issued in its prosecution, while not completely forthcoming, did not rise to the level of inequitable conduct.

With respect to the Byk Gulden patent, Teva and Dr. Reddy's argue that Eisai's failure to disclose this reference to the Patent Office during prosecution of the '552 patent was material because a reasonable examiner would have used it to issue a new and stronger prima facie obviousness rejection on the basis of Byk Gulden's disclosure of asymmetrically-substituted compounds having a methoxyethoxy at the 4-position of the pyridine ring. But the district court found Byk Gulden's teachings cumulative with references already disclosed to the Patent Office (Junggren or Junggren combined with Beecham). As per 37 C.F.R. § 1.56, cumulative evidence is definitionally not material evidence. *See Monsanto Co. v. Bayer Bioscience N.V.*, 514 F.3d 1229, 1237 (Fed.Cir.2008). Here, the Junggren reference specifically disclosed asymmetrically substituted compounds, including a compound having a 4-position methoxyethoxy substituent. Thus the Byk Gulden reference offered nothing new to the record already before the Patent Office. And even Teva's expert conceded Byk Gulden would not have provided the examiner with anything new. *Id.* at 57.

Thus the district court was well within its discretion in concluding that the Byk Gulden patent was not material to the prosecution of the '552 patent. Even if Byk Gulden had been material, the lack of clear and convincing evidence of intent to deceive would nonetheless have imposed an insurmountable bar to finding inequitable conduct, for the reasons given by the district court.

As for the Fujisaki Declaration, Eisai submitted it during prosecution to overcome an obviousness rejection. Because this reference shows rabeprazole's pharmacological properties, the trial court found it highly material. *Id.* at 59. Teva ***1362** and Dr. Reddy's argue that the data presented in the Fujisaki Declaration were misleading. They contend that the comparison with two non-prior art compounds without a comparison of the ethyl homolog of rabeprazole, SHKA 661, sent the examiner on a dead-end side trip. The district court properly characterized this argument as "contorted." *Id.* The Fujisaki Declaration indisputably showed a comparison between rabeprazole and the prior art compound called out by the examiner, demonstrating rabeprazole's superiority. Further, as discussed above, the materiality of SHKA 661 and the patent application claiming it was low. The data from the Fujisaki Declaration were relevant to prosecution, but Eisai had no obligation to include additional, unnecessary data such as a comparison to SHKA 661. Thus the district court did not abuse its discretion in concluding that Eisai did not commit inequitable conduct in failing to include additional data in the Fujisaki Declaration to the examiner. Even here, where the submission to the Patent Office itself was highly material to prosecution, the lack of deceptive intent rendered stillborn yet another allegation of inequitable conduct.

Finally, Teva and Dr. Reddy's assert that that Eisai deceptively declined to inform the examiner of a patent application for lansoprazole, a prior art proton pump inhibitor (and the active ingredient in Prevacid). The district court disposed of this argument on summary judgment. The district court found that Teva and Dr. Reddy's had presented neither direct evidence of deceptive intent nor any evidence to support an inference of materiality. *SJ Enforceability Order* at 58. The strongest evidence of some problem was the passing comment of one Eisai "insider" that the similarity of lansoprazole and rabeprazole "bothers me." *Id.* at 59. But this vague, subjective statement is not sufficient by any means to establish materiality, let alone intent. Moreover, given lansoprazole's fluorinated substituent and its resultant impotence to render the '552 patent invalid, the district court properly rejected this strained theory of inequitable conduct on summary judgment.

IV

In a series of thoughtful, thorough opinions, the district court carefully explained its reasoning with respect to both obviousness and inequitable conduct. Because the district court properly concluded that Teva and Dr. Reddy's failed to prove that the '552 patent was invalid for obviousness or unenforceable for inequitable conduct, this court affirms the district court's judgment.

AFFIRMED

COSTS

Each party shall bear its own costs.

C.A.Fed. (N.Y.),2008.
Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.
533 F.3d 1353, 87 U.S.P.Q.2d 1452

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